ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

# Evaluation of the Knowledge of Women of Childbearing Age with Epilepsy about the Impact of Their Disease in Contraception, Pregnancy and Breastfeeding: A Multicenter Cross-Sectional Study

# Avaliação do Conhecimento das Mulheres com Epilepsia em Idade Fértil sobre o Impacto da sua Doença na Contraceção, Gravidez e Amamentação: Um Estudo Transversal Multicêntrico

Pedro LOPES DAS NEVES✉[1], Rita VENTURA[2], André SOBRAL-PINHO[2], Elisa SILVA[3], Afonso MORGADINHO[3], Joana VITOR[4], Miguel MIRANDA[5], Beatriz MADUREIRA[1], Joana MONIZ DIONÍSIO[1], Rita PINHEIRO[1], Sofia DELGADO[1], Duarte CARAPINHA[1], André REGO[1], Francisca SÁ[2], Maria Rita PELEJÃO[2], Francisco ANTUNES[3], Inês MARQUES[3], Vanessa BRITO DA SILVA[4], Sandra CASTRO SOUSA[5], João PERES[1], António MARTINS[1], Raquel TOJAL[1]
**Acta Med Port 2023 Jun;36(6):383-393** ▪ https://doi.org/10.20344/amp.19156

## ABSTRACT

**Introduction:** The interaction of antiseizure medication with contraceptives, its potential teratogenicity and implications in pregnancy and breastfeeding are aspects to consider in the neurological care of women with epilepsy of childbearing age. To ensure the commitment in therapeutic decisions and the appropriate planning of maternity, it is essential that women are informed about the implications of their disease in these domains. The main aim of this study was to assess the knowledge of women of childbearing age with epilepsy concerning the impact of epilepsy in contraception, pregnancy and breastfeeding. As secondary aims we defined (1) the demographic, clinical and therapeutic characterization of this group of patients, (2) the identification of variables that correlated with the level of knowledge of women with epilepsy, and (3) the identification of preferential methods to acquire new knowledge about epilepsy.

**Methods:** The study was observational, cross-sectional and multicentric, and was carried out in five hospitals of the Lisbon metropolitan area. After identifying all women of childbearing age with epilepsy followed in the epilepsy clinic of each center, we applied an electronic questionnaire based on a non-systematic review of the literature.

**Results:** One hundred and fourteen participants were validated, with a median age of 33 years. Half of the participants were on monotherapy, and the majority had no seizures in the last six months. We identified important gaps in the participants' knowledge. Sections about complications and administration of antiseizure medication during pregnancy were the ones with the worst results. None of the clinical and demographic variables correlated with the final questionnaire score. Having had a previous pregnancy and the desire to breastfeed in a future pregnancy were positively correlated with the performance in breastfeeding section. Face-to-face discussion during medical outpatient visits was selected as the preferential method to learn about epilepsy, and the internet and social media were the least preferred ones.

**Conclusion:** The knowledge of women of childbearing age with epilepsy in the Lisbon metropolitan area concerning the impact of epilepsy in contraception, pregnancy and breastfeeding seems to have significant gaps. Medical teams should consider engaging in patient education particularly during outpatient clinics.

**Keywords:** Anticonvulsants; Breast Feeding; Contraception; Epilepsy/drug therapy; Health Knowledge, Attitudes, Practice; Pregnancy; Surveys and Questionnaires; Teratogenesis

## RESUMO

**Introdução:** A interação dos fármacos anticrise epilética com os métodos contracetivos, a sua potencial teratogenicidade e as implicações na gravidez e amamentação são aspetos a considerar no acompanhamento de mulheres com epilepsia em idade fértil. Para o seu desejado envolvimento nas decisões terapêuticas e o adequado planeamento da maternidade, é essencial que as mulheres estejam corretamente informadas acerca das implicações da sua doença. O objetivo principal do presente estudo foi avaliar o conhecimento das mulheres com epilepsia em idade fértil sobre o impacto da epilepsia na contraceção, gravidez e amamentação. Como objetivos secundários definiram-se (1) a caracterização demográfica, clínica e terapêutica deste grupo de doentes, (2) a identificação de variáveis correlacionadas com o nível de conhecimento das mulheres com epilepsia, e (3) a identificação de meios e suportes preferenciais para aquisição de novos conhecimentos sobre epilepsia.

**Métodos:** O estudo foi observacional, transversal e multicêntrico, tendo decorrido em cinco centros hospitalares da região metropolitana de Lisboa. Após identificação das mulheres com epilepsia em idade fértil seguidas na Consulta de Epilepsia de cada centro, aplicou-se um questionário eletrónico construído após revisão não sistemática da literatura.

**Resultados:** Foram validadas 114 participantes, com uma idade mediana de 33 anos. Metade das participantes apresentavam-se sob monoterapia, tendo a maioria a epilepsia controlada há pelo menos seis meses. Identificaram-se importantes lacunas no conhecimento das participantes. Conceitos sobre complicações dos fármacos anticrise epilética e a sua administração durante a gravidez motivaram piores resultados. Não houve correlação entre variáveis clinico-demográficas e o resultado no questionário. A ocorrência de gravidez prévia e o desejo de amamentar numa gravidez futura correlacionaram-se com o desempenho na secção sobre amamentação. A discussão oral na consulta foi a forma preferencial para aquisição de novos conhecimentos sobre epilepsia, tendo a internet e as redes sociais sido os meios menos escolhidos.

1. Serviço de Neurologia. Hospital Professor Doutor Fernando Fonseca. Amadora. Portugal.
2. Serviço de Neurologia. Centro Hospitalar Lisboa Ocidental. Lisboa. Portugal.
3. Serviço de Neurologia. Hospital Garcia de Orta. Almada. Portugal.
4. Serviço de Neurologia. Hospital Beatriz Ângelo. Loures. Portugal.
5. Serviço de Neurologia. Hospital de Cascais Dr. José de Almeida. Cascais. Portugal.
✉ **Autor correspondente:** Pedro Lopes das Neves. pedrolopesneves@gmail.com
**Recebido/*Received*:** 05/10/2022 - **Aceite/*Accepted*:** 31/01/2023 - **Publicado *Online*/*Published Online*:** 28/03/2023 - **Publicado/*Published*:** 01/06/2023

**Conclusão:** O conhecimento das mulheres com epilepsia em idade fértil na área metropolitana de Lisboa sobre o impacto da sua doença na contracepção, gravidez e amamentação parece apresentar lacunas importantes. A educação para a saúde deste grupo deverá constituir uma preocupação por parte das equipas médicas, devendo privilegiar-se a consulta como local de ensino.
**Palavras-chave:** Aleitamento Materno; Anticonvulsivantes; Conhecimentos, Atitudes e Prática em Saúde; Contracepção; Epilepsia/tratamento farmacológico; Gravidez; Inquéritos e Questionários; Teratogénese

## INTRODUCTION

An estimated 20,000 women are currently affected by epilepsy in Portugal, according to the Portuguese League Against Epilepsy (*Liga Portuguesa Contra Epilepsia* - LPCE), including around half of these of childbearing age,[1] in need for specialised neurological care considering the impact of epilepsy and treatment on specific aspects of health. Contraception, the impact on pregnancy, the teratogenicity of antiepileptic drugs (AEDs) and their interference with breastfeeding should be considered when taking care of these patients in neurology consultations.[2]

The information regarding the impact of this condition is crucial to ensure that women of childbearing age actively participate in treatment decisions and adequately plan their pregnancies. These patients must be made aware of enzyme-inducing AEDs that reduce the effectiveness of oral contraceptives,[3-5] AEDs such as sodium valproate (VPA), with known teratogenic effects,[6-8] the importance of controlling seizures before pregnancy and especially during pregnancy,[9,10] and breastfeeding.[11]

Different studies carried out in other countries have assessed the knowledge of women with epilepsy (WWE) regarding the impact of their disease. Suboptimal knowledge of the interaction between AEDs and oral contraceptives, in addition to their potential teratogenic effects, has been found in a 2009 study by Pack involving 148 WWE followed at a North-American clinic who have responded to a questionnaire.[12] A questionnaire was responded by 100 WWE at a Canadian tertiary clinic in a study by Metcalfe, carried out in 2012, showing that women's knowledge about the impact of epilepsy on pregnancy was also low.[13] Finally, in a 2018 study, Dierking applied a similar methodology to 179 WWE of childbearing age, mostly of German nationality, and found that 38% of women on enzyme-inducing AEDs were unaware of its interaction with oral contraceptives and 41% of women medicated with VPA were unaware of its potential teratogenicity,[14] in line with previous studies.

A 2014 meta-analysis by McGrath including 12 studies assessing the knowledge of WWE on this subject (using questionnaires and/or interviews) found that even though they were aware of many of the topics, they had limited real knowledge about the implications of epilepsy in pregnancy and breastfeeding. The review also reached the conclusion that many patients described suboptimal information regarding their condition.[15]

No previous Portuguese studies have assessed the knowledge of Portuguese women with epilepsy on these subjects. This study was aimed at assessing the knowledge of women of childbearing age in our community regarding the impact of epilepsy and treatment in the following five domains: (1) contraception; (2) pregnancy intention; (3) teratogenicity of AEDs; (4) pregnancy complications; and (5) breastfeeding. The secondary aims included (1) the assessment of the demographic, clinical and therapeutic pattern of the disease in this group; (2) the identification of variables that correlated with the level of knowledge of WWE in those domains and (3) the identification of the preferred means and supports for acquiring new knowledge on these subjects.

## METHODS

This was an observational, cross-sectional and multicentric study aimed at assessing the knowledge of WWE of childbearing age by using an electronic questionnaire. It was divided into two stages, including (i) a first stage held throughout July and August 2021 in a single hospital centre [*Hospital Professor Doutor Fernando Fonseca* (HFF)] and, (ii) in a second stage, throughout January and February 2022, extended to four other hospitals [*Centro Hospitalar Lisboa Ocidental* (CHLO), *Hospital Garcia de Orta* (HGO), *Hospital Beatriz Ângelo* (HBA) and *Hospital de Cascais Dr. José de Almeida* (HC)]. Together, these hospitals have a catchment area of 11 municipalities: Lisbon (western region, four parishes) and Oeiras (CHLO); Amadora and Sintra (HFF); Cascais (HC); Loures, Mafra, Odivelas and Monte Agraço (HBA); and Almada and Seixal (HGO). These include a reference clinic for refractory epilepsy (CHLO). The study was approved by the Ethics Committee of all the hospitals involved.

All patients attending one of the five hospitals and meeting the following criteria were included in the study: (1) female patients, (2) aged 18-45, (3) attending an epilepsy clinic at the time of recruitment (first week of each study period), (4) diagnosed with epilepsy by a neurologist (patients with a history of epilepsy and adequate seizure control were not considered), and (5) with access to a computer and email address. Patients not fluent in Portuguese and those presenting with intellectual disabilities or cognitive impairments preventing from responding the electronic questionnaire were excluded from the study.

Based on the hospital medical records, the patients who met the inclusion criteria were contacted by phone. A telephone script was developed for this contact, explaining the

purpose of the study, and asking for an email address. If there was no response to the first contact, at least one further attempt was made. No further recruitment procedures were used. An email containing a link to the electronic questionnaire and the attached informed consent was subsequently sent to the address provided by each participant.

The questionnaire was developed during the first stage of the study using the Google Forms® platform upon identification of similar studies in literature.[12-18] A questionnaire was constructed, divided into three parts: (1) demographic and clinical characteristics of each respondent (demographic characteristics, epilepsy and treatment characteristics, contraceptive methods, previous pregnancy or plans for future pregnancy and intention to breastfeed); (2) application of a scale (developed by the authors) designed to assess the respondent's knowledge of epilepsy. Four statements were presented for each of the five domains, rated on a five-point Likert scale. The highest two points were considered correct when the statement was true ("strongly agree" or "agree"), or the lowest two points when it was false ("strongly disagree" or "disagree"). For example, for a statement considered as true ("I think it's important discussing with the neurologist the method for not getting pregnant"), "strongly agree" or "agree" responses were considered correct. The correct responses were based on literature, namely scientific reviews and guidelines[1-11,19-26]; (3) acquisition of new knowledge (a question ranking the preferred means of acquiring information about the disease, including "consultation", "email", "information leaflets", "website" or "social networks"). Basic validity of the information entered via the electronic platform was carried out to ensure its quality (e.g., mandatory response to all items, only one response per item), and only one response per participant was allowed (by entering a unique authentication code provided in the email sent to each participant). The questionnaire that was applied was not validated and is available as Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19156/15093).

A descriptive analysis of the patients' demographic and clinical variables was carried out. Performance on the epilepsy knowledge assessment scale (second part of the questionnaire) was assessed by calculating the mean and standard deviation of correct answers per question, per group of questions and for the total number of items. Whenever a coefficient of variation > 50% was found, the median was added as a measure of central tendency. Mean correct responses were compared between groups using Student's *t*-test or one-way ANOVA to identify variables associated with better performance on this scale. Whenever distributions were not normal (according to the Shapiro-Wilk test), non-parametric tests were applied instead (Mann-Whitney test for comparisons between two groups and Kruskal-Wallis for comparisons between multiple groups). Pearson's correlation coefficient was obtained to assess the correlation between age or time since epilepsy was diagnosed and the score on the epilepsy knowledge assessment scale. Significance levels < 0.05 were considered as significant. Microsoft Excel® (version 16) was used to pre-process the variables and RStudio® (version 1.3.959) software, both for Macintosh®, were used for the statistical analysis.

## RESULTS

### Participation rate; demographic and clinical characteristics of our group of patients

A total of 466 WWE of childbearing age attended the five hospitals within the study period, 107 out of these could not be reached by phone and 81 were excluded from the study as these presented with an intellectual disability; considering the 278 WWE of childbearing age who were contacted by phone, 17 did not have access to a computer or email, 17 refused to participate and 130 agreed but did not complete the questionnaire. A response rate of 41% was obtained, corresponding to 114 respondents (Fig. 1), with a median age of 33 years and 84.2% with secondary education or above. Epilepsy was diagnosed 13 years (median value) before the completion of the questionnaire. Half of the patients were receiving monotherapy (50.0%), mostly with levetiracetam and lamotrigine. Around 37% of the patients were on enzyme-inducing drugs, and only 13 patients (11.4%) on VPA. Around 69% of the respondents had been seizure free for more than six months (Table 1).

As regards family planning options, oral contraception was most frequently used (38.6%) and no contraception was described by only 30.7% of the participants. Oral contraception was mostly used by 18 of the 42 patients (42.9%) on enzyme-inducing drugs, while three patients on VPA did not use any contraceptive method.

Around half of the patients (52.6%) have described a previous pregnancy. Only 14 patients (12.3%) have described a pregnancy intention throughout the following year, and five of them presented with uncontrolled epilepsy with at least one seizure episode every two or three months. Ninety-five participants (83.3%) have described the intention to breastfeed.

### Evaluation of the performance on the epilepsy knowledge assessment scale

On average, a 49.5% (± 17.7%) correct response rate and an 11.2% (± 9.4%; median 10%) incorrect response rate have been found regarding the epilepsy knowledge assessment scale; the participants chose neither to agree nor disagree with the statements presented in 39.3% (± 21.3%; median 35%) of the questions.

A hit rate for each section of the scale between 59.6%

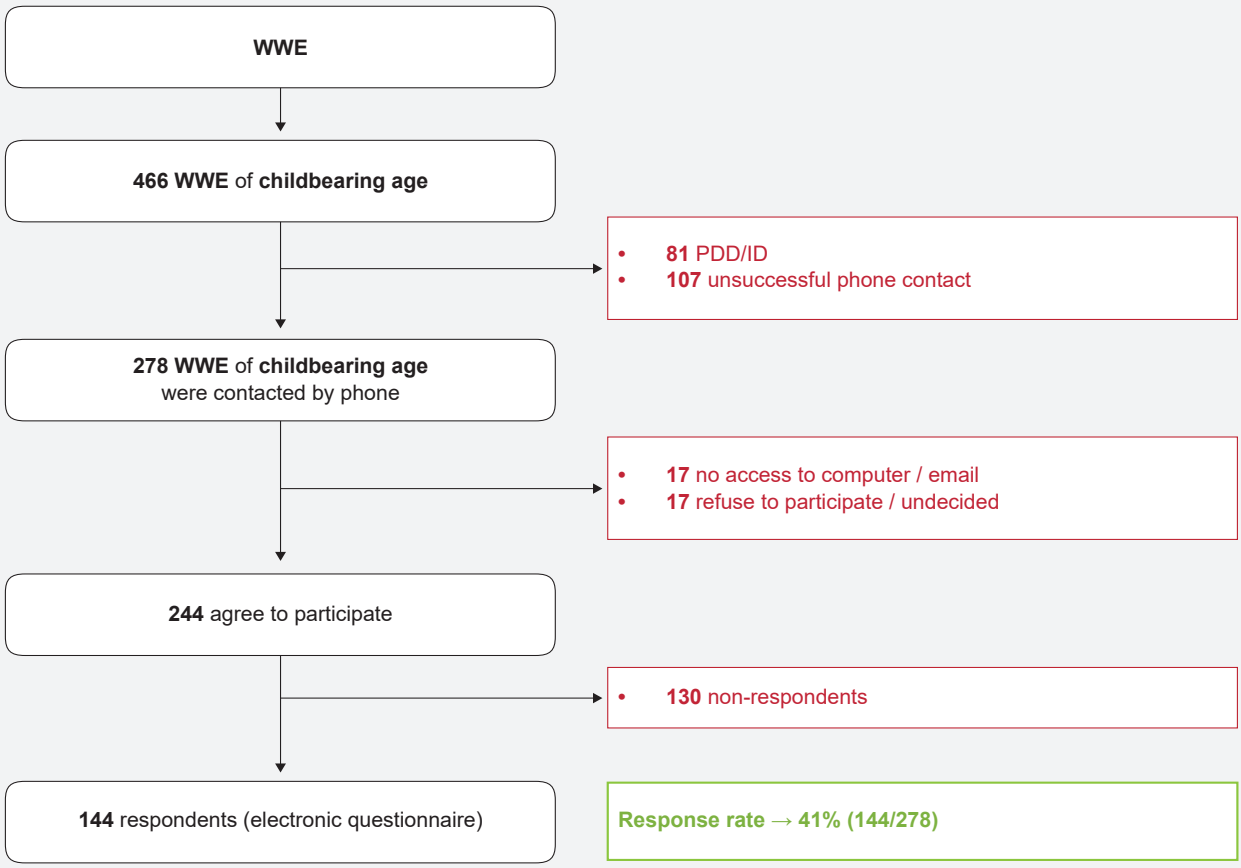


Figure 1 – Analysis of the selection and participation of WWE of childbearing age
PDD: psychomotor developmental delay; EC: epilepsy consultation; WWE: women with epilepsy; ID: intellectual disability

and 41% has been found [Contraception: 59.6% (± 28.3%; median 75%); Pregnancy intention 54.8% (± 25.1%), Breastfeeding 47.1% (± 31.3%; median 50%); AEDs in pregnancy 44.7% (± 27.3%; median 50%), Pregnancy complications 41% (± 26.2%; median 50%)], as shown in Fig. 2.

The following results are worth mentioning: (1) even though 69.3% of the participants have considered discussing the contraceptive method with the neurologist as relevant, 57.1% of the WWE did not recognise the intrauterine device (IUD) as an effective contraceptive method in WWE treated with EADs; (2) most WWE (80.7%) have recognised the relevance of planning their pregnancy with the support of the neurologist, even though only 27.2% have recognised the relevance of an adequate disease control within the nine months prior to conception; (3) 20.2% of the participants disagreed and 49.1% neither agreed nor disagreed with the possible need to increase the dose of EADs during pregnancy; (4) 21.1% have considered that vaginal delivery is contraindicated in WWE; (5) only around half (51.8%) of the patients have acknowledged that breastfeeding is not contraindicated when on AEDs, while 12.3% even described that AEDs should be discontinued if they wanted to breastfeed their babies. The individual responses to each of the 20 items are shown in Fig. 2.

**Identification of variables associated with better performance on the epilepsy knowledge assessment scale**

No variables were significantly associated with better performance on the final score of the scale, highlighting the fact that age ($p$ = 0.28), higher education ($p$ = 0.21) and disease duration ($p$ = 0.13) were not associated with better scores (Table 3).

An additional attempt was made to identify variables associated with better performance in specific domains and questions in the scale: (1) a previous pregnancy ($p$ = 0.004) and breastfeeding intention in a future pregnancy ($p$ = 0.003) were associated with higher scores in “Breastfeeding” section; (2) pregnancy intention (or current pregnancy) was associated with better performance in “Pregnancy intention” section, ($p$ = 0.03); (3) treatment with VPA was

Table 1 – Characteristics of our group of patients, according to the demographic data, the type of epilepsy and treatment, contraception, and pregnancy intention

| Group | Variable | |
|---|---|---|
| General characteristics | **Number of participants** (n) | 114 |
| | **Age** [median in years, (interquartile range)] | 33 (13) |
| | **Education** [n, (%)] | |
| | Primary | 2 (1.8) |
| | Basic (lower secondary) | 16 (14.0) |
| | Secondary | 42 (36.8) |
| | Higher | 54 (47.4) |
| Epilepsy characteristics | **Disease duration** [median (years), (interquartile range)] | 13 (13) |
| | **Number of AEDs used** [n, (%)] | |
| | None | 12 (10.5) |
| | 1 | 57 (50.0) |
| | 2 | 27 (23.7) |
| | 3 | 12 (10.5) |
| | 4 | 4 (3.5) |
| | 5 | 2 (1.8) |
| | **AED** [n, (%)] | |
| | Levetiracetam | 67 (58.8) |
| | Lamotrigine | 29 (25.4) |
| | Sodium valproate | 13 (11.4) |
| | Other AEDs | 43 (37.7) |
| | Enzyme-inducing AEDs | 42 (36.8) |
| | **Type of seizures** [n, (%)] | |
| | Absence seizures | 47 (41.2) |
| | Tonic-clonic seizures | 21 (18.4) |
| | Myoclonic | 7 (6.1) |
| | Focal | 12 (10.5) |
| | Others | 18 (15.8) |
| | Undetermined | 42 (36.8) |
| | **Seizure control** [n, (%)] | |
| | No seizures over the past 6 months | 79 (69.3) |
| | 1 seizure episode at each 2-3 weeks | 12 (10.5) |
| | 1 seizure per month | 10 (8.8) |
| | 1 seizure per week | 5 (4.4) |
| | > 1 seizure per week | 8 (7.0) |
| Family planning | **Contraception** [n, (%)] | |
| | Oral | 44 (38.6) |
| | IUD | 14 (12.3) |
| | Implants | 10 (8.8) |
| | Condoms | 10 (8.8) |
| | Does not know/does not respond | 1 (0.01) |
| | No contraception | 35 (30.7) |
| | **Previous pregnancy** [n, (%)] | |
| | No | 54 (47.4) |
| | Yes | 60 (52.6) |
| | **Planned previous pregnancy** [n, (% patients with previous pregnancy)] | |
| | Only planned pregnancies | 32 (53.3) |
| | At least one non-planned pregnancy | 28 (46.7) |
| | **Number of children** [n, (%)] | |
| | No children | 58 (50.9) |
| | 1 | 25 (21.9) |
| | 2 | 26 (22.8) |
| | 3 | 5 (4.4) |
| | 4 or above | 0 (0.0) |
| | **Pregnancy intention** [n, (%)] | |
| | Pregnancy intention | 14 (12.3) |
| | No pregnancy intention | 97 (85.1) |
| | Pregnant | 3 (2.6) |
| Breastfeeding | **Breastfeeding intention** [n, (%)] | |
| | Breastfeeding intention | 95 (83.3) |
| | No breastfeeding intention | 4 (3.5) |
| | Does not know | 15 (13.2) |

IUD: intrauterine device; AED: antiepileptic drug; n: absolute number

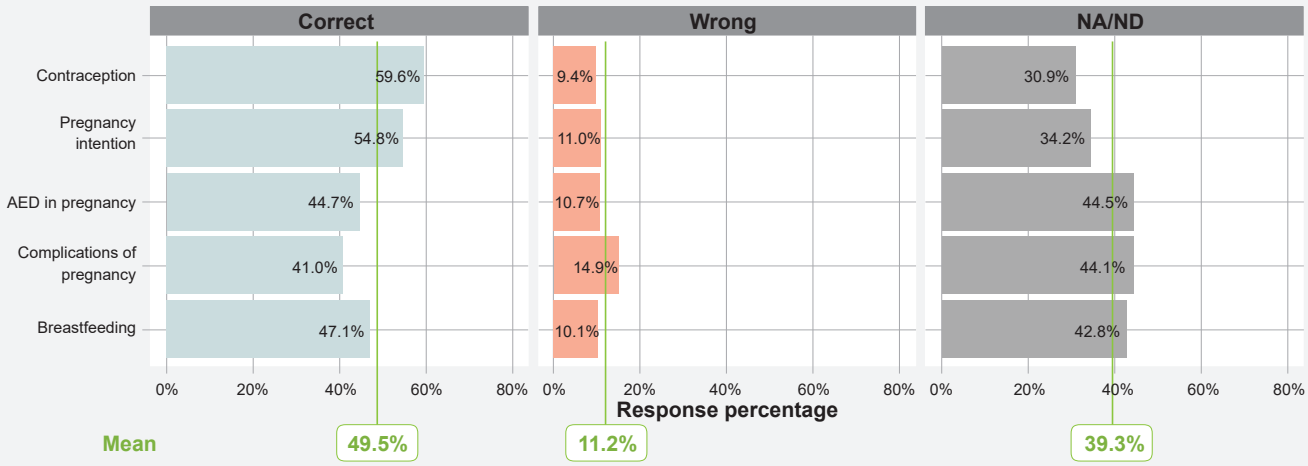


Figure 2 – Responses in the epilepsy knowledge scale
AED: antiepileptic drugs; NA/ND: neither agree / nor disagree

associated with better results in the item related to teratogenicity of this drug ($p$ = 0.02).

No significant differences were found in the responses of patients on enzyme-inducing AEDs to the question on the influence of AEDs on the efficacy of the contraceptive pill.

**Preferred methods of acquiring new knowledge of the disease**

When asked about their preferred method for acquiring new knowledge of epilepsy, neurology consultations were preferred by 74.6% of the participants over other methods including email, websites, or social networks. Social networks were considered as the last out of the five options presented, by 68.4% of the participants (Fig. 3).

## DISCUSSION

As far as we know, this was the first Portuguese multicentric study assessing the knowledge of WWE of the implications of their disease and treatment on contraception, pregnancy, and breastfeeding.

Significant gaps were found regarding the respondents' performance on the knowledge assessment scale. In around half of the questions, WWE have described not knowing how to define the statements presented, or that these were classified incorrectly. These results are in line with what has been described in other studies: Dierking's study has shown that only 46% of the items related to the impact of epilepsy on pregnancy were correctly responded[14]; Metcalfe showed a slightly lower rate of correct answers (40%)[13]; Pack's study has found that 65% of patients on enzyme-inducing AEDs were unaware of the loss of efficacy of oral contraceptives and that 40% of WWE receiving category D EADs were unaware of its potential effect on the foetus.[12] The comparison of our results with previous studies must be made with caution, as described in a previous study,[14] on the one hand because the follow-up of WWE may not be carried out in a specific consultation in some healthcare systems (as in our group of patients), and on the other hand due to the fact that the evolution of evidence and the recommendations of scientific societies may change the interpretation of the responses to some of the items.

When analysing the responses by group, "Pregnancy complications", "AEDs in pregnancy" and "Breastfeeding" groups were those that showed the worst performance. Special care should be taken on delivering knowledge in these areas.

Relevant findings regarding the pattern of AEDs use, seizure control and the use of contraceptive methods in this population have been found in our group of patients:

- In accordance with current international recommendations, the present study showed neurologists' preference for monotherapy regimens and the preferential use of AEDs with lower teratogenic potential in WWE of childbearing age, including levetiracetam and lamotrigine.[6] The use of VPA was residual given its known teratogenic risk, and most of these patients were using some form of contraception.[7] It is also worth mentioning the higher performance that was found in patients on VPA when compared to the remaining patients, as regards the item related to the teratogenicity of VPA, even though corresponding to an accuracy rate lower than 50%;
- Around seven out of ten patients presented with controlled epilepsy and no seizures for at least six months, which is a good prognostic indicator of seizure-free during a future pregnancy.[9] However, five

Table 2 – Responses in the epilepsy knowledge scale

| **Section** (references) | **Subject** | **Statement** (correct response: SA/A, SD/D) | **Scoring** n = 114 (%) | | |
|---|---|---|---|---|---|
| | | | correct | wrong | NA/ND |
| Contraception[1–5,19] | Relevance of a follow-up by a neurologist | "*Acho importante discutir o método para não engravidar com o meu neurologista*" - "The discussion of the contraceptive method with my neurologist is a relevant issue to me" [SA/A] | 69.3 | 7.9 | 22.8 |
| | Influence of AED on the pill | "*Os medicamentos para a epilepsia podem influenciar a pílula*" - "Antiepileptic drugs could have an influence on the pill" [SA/A] | 50.0 | 21.9 | 28.1 |
| | Efficacy of IUD with AED | "*O dispositivo intrauterino não é eficaz se tomar medicamentos para a epilepsia*" - "Intrauterine devices are not effective when you are taking antiepileptic drugs" [SD/D] | 43.0 | 5.3 | 51.8 |
| | Efficacy of barrier methods with AED | "*Os métodos de barreira como o preservativo são eficazes, mesmo se tomar medicamentos para a epilepsia*" - "Barrier methods such as condoms are effective, even when taking antiepileptic drugs" [SA/A] | 76.3 | 2.6 | 21.1 |
| Pregnancy intention[2,9–11,20] | Pregnancy planning with a neurologist | "*Acho importante planear a gravidez com o meu neurologista*" - "Pregnancy planning with my neurologist is an important issue to me" [SA/A] | 80.7 | 6.1 | 13.2 |
| | Importance of folic acid | "*Tomar ácido fólico antes de engravidar ajuda a prevenir malformações no meu bebé*" - "Taking folic acid before pregnancy prevents birth defects" [SA/A] | 64.9 | 5.3 | 29.8 |
| | Importance of controlled epilepsy | "*Não ter crises nos 9 meses antes de engravidar diminui o risco de ter crises quanto estiver grávida*" - "No seizures within the 9 months previous to pregnancy reduces the risk of having seizures throughout pregnancy" [SA/A] | 27.2 | 22.8 | 50.0 |
| | Controlled disease before conception | "*Antes de engravidar, é mais seguro para o meu bebé reforçar a medicação com mais um medicamento para a epilepsia*" - "Before getting pregnant, is it safer for my baby to increase the medication with another antiepileptic drug" [SD/D] | 46.5 | 9.6 | 43.9 |
| AED in pregnancy[1,2,6–8,21–24] | Keeping AED during pregnancy | "*Se ficar grávida, devo parar de imediato os medicamentos para a epilepsia*" - "If I become pregnant, I should stop epilepsy medication immediately" [SD/D] | 71.1 | 5.3 | 23.7 |
| | Need for a dose adjustment during pregnancy | "*Pode ser necessário aumentar a dose dos medicamentos para a epilepsia ao longo da gravidez*" - "Epilepsy medication may have to be increased during pregnancy" [SA/A] | 30.7 | 20.2 | 49.1 |
| | Teratogenic risk of AED | "*Alguns medicamentos para a epilepsia aumentam o risco de malformações no bebé*" - "The risk of birth defects is increased with the use of some antiepileptic drugs" [SA/A] | 56.1 | 5.3 | 38.6 |
| | Teratogenic risk of VPA | "*A toma de VPA durante a gravidez previne a redução do QI da criança causada por outros medicamentos para a epilepsia*" - "Taking VPA during pregnancy prevents the reduction in the child's IQ caused by other antiepileptic drugs [SD/D] | 21.1 | 12.3 | 66.7 |
| Pregnancy complications[2,9,24] | Risk of low birth weight and preterm delivery | "*As mães que tomam medicamentos para a epilepsia estão em maior risco de ter bebés de baixo peso e de ter um parto antes do final da gravidez*" - "Mothers on antiepileptic drugs are at greater risk of delivering low birthweight babies and giving birth before the end of pregnancy" [SA/A] | 20.2 | 24.6 | 55.3 |
| | Vaginal delivery viability | "*O parto por via vaginal está contraindicado na mulher com epilepsia, sendo mais segura a cesariana*" - "Vaginal deliveries are contraindicated in women with epilepsy, while C-sections are safer" [SD/D] | 40.4 | 21.1 | 38.6 |
| | Risk of bleeding, pregnancy-induced hypertension and pre-eclampsia | "*O risco de hemorragia tardia na gravidez, pré-eclâmpsia e HTA associada à gravidez está substancialmente aumentado na MCE*" - "The risk of vaginal bleeding during late pregnancy, pre-eclampsia and pregnancy-induced hypertension is substantially increased in WWE" [SD/D] | 28.9 | 8.8 | 62.3 |
| | Chance of problem-free pregnancy | "*Seguindo os conselhos do meu neurologista, é muito provável que a minha gravidez decorra sem problemas*" - "Following my neurologist's advice, it's very likely that my pregnancy will go smoothly" [SA/A] | 74.6 | 5.3 | 20.2 |
| Breastfeeding[2,11,25,26] | AED during breastfeeding | "*Devo parar os medicamentos para a epilepsia antes de iniciar a amamentação*" - "I should stop epilepsy medication before starting breastfeeding" [SD/D] | 54.4 | 12.3 | 33.3 |
| | AED elimination in breast milk | "*A maioria dos medicamentos para a epilepsia é excretada no leite materno*" - "Most antiepileptic drugs are eliminated in breast milk" [SA/A] | 27.2 | 14.0 | 58.8 |
| | Effects of breastfeeding on child development | "*Os bebés amamentados por MCE a realizar medicação para a epilepsia têm mais dificuldades de aprendizagem na escola*" - "Babies breastfed by WWE taking epilepsy medication present with more learning difficulties at school" [SD/D] | 55.3 | 4.4 | 40.4 |
| | Breastfeeding is not contraindicated | "A *amamentação está contraindicada nas mulheres a realizar medicamentos para a epilepsia*" - "Breastfeeding is contraindicated in women taking epilepsy medication" [SD/D] | 51.8 | 9.6 | 38.6 |

SA/A: strongly agree/agree; SD/D: strongly disagree/disagree; NA/ND: neither agree/nor disagree. WWE: women with epilepsy (MCE: *mulheres com epilepsia*)
**Note**: References presented above explain the correct responses to the items. The correct response to each item is shown between brackets.

Table 3 – Variables associated to higher performance in responding the questionnaire

| Questionnaire scoring | Variable | Ratio of correct responses [mean, 0% - 100%] | |
|---|---|---|---|
| Total [20 items] | Age | r = 0.10 | *p* = 0.28 |
| | Education | Primary – 72.5<br>Basic (lower secondary) – 47.2<br>Secondary – 48.0<br>Higher – 50.5 | *p* = 0.21 |
| | Disease duration | r = 0.14 | *p* = 0.13 |
| | Number of AED | No AED – 53.8<br>1 or more AED – 49.0 | *p* = 0.20 |
| | Previous pregnancy | Yes – 51.8<br>No – 46.9 | *p* = 0.13 |
| | Pregnancy intention | Pregnancy intention OR pregnant – 52.9<br>No pregnancy intention – 48.9 | *p* = 0.61 |
| "Pregnancy intention" [4 items] | Pregnancy intention | Pregnancy intention OR pregnant – 66.2<br>No pregnancy intention – 52.8 | ***p* = 0.03** |
| "Complications of pregnancy" [4 items] | Previous pregnancy | Yes – 45.0<br>No – 36.6 | *p* = 0.08 |
| "Breastfeeding" [4 items] | Breastfeeding intention | Breastfeeding intention – 51.1<br>No breastfeeding intention OR does not know – 27.6 | ***p* = 0.003** |
| | Previous pregnancy | Yes – 55.0<br>No – 38.4 | ***p* = 0.004** |
| "Teratogenicity of valproate" ["AED in pregnancy" – Q4] | Taking sodium valproate | Yes – 46.2<br>No – 17.8 | ***p* = 0.02** |
| "Interaction of AED with oral contraceptives" ["Contraception" – Q2] | Taking enzyme-inducing AED | Yes – 52.4%<br>No – 48.6% | *p* = 0.70 |

AED: antiepileptic drug; Qx: item number x.
**Note**: Statistically significant results are presented in bold.

of the patients who described an intention to become pregnant within the following year did not present with controlled epilepsy;

- Oral contraceptives were the most common method of contraception used by WWE. Despite the higher risk of contraceptive failure, almost half of the patients on enzyme-inducing drugs have described the use of oral contraceptives. In this group, the use of other contraceptive methods is recommended.[3-5]

The fact that no variables associated with greater knowledge of epilepsy were identified (namely age, education, disease duration, number of AEDs, previous pregnancy, or pregnancy intention) may reflect the study's weak power. However, by reflecting a real characteristic of this population, this is an alert to the physicians as regards the need to address all these topics with the patients, regardless of the personal and obstetric history or education. Even though education was associated with greater knowledge of the disease, no association was found in the Canadian study described above between disease duration, polytherapy or previous pregnancy and the final score in the assessment scale.[13]

The better performance in the "Breastfeeding" section of respondents with previous pregnancies should reflect the knowledge acquired during these. On the other hand, the better performance of respondents who intended to breastfeed or to get pregnant (or were already pregnant) in the "Breastfeeding" or "Pregnancy intention" sections, respectively, may correspond to an active search for information by WWE who plan to make these choices in the future, although a reverse causality cannot be ruled out (i.e., patients who are better informed about the possibility of breastfeeding may therefore wish to do so).

Contrary to our previous expectations, social networks or the Internet were not the preferred means of acquiring new knowledge, and there is a preference for the approach to these topics within a neurology consultation. This may reflect the stigma associated with epilepsy, with WWE preferring an approach within a confidential and safe environment.

Some biases may have existed and should be discussed. As regards a selection bias, the fact that only patients with access to a computer and an email address were included, in addition to the fact that basic computer skills were required, as well as a successful initial telephone contact based on updated personal data in the hospital file, together with the fact that responding medical questionnaires is more common in patients who are more concerned about their health, may have contributed to increasing the hit rate on the epilepsy knowledge assessment scale.

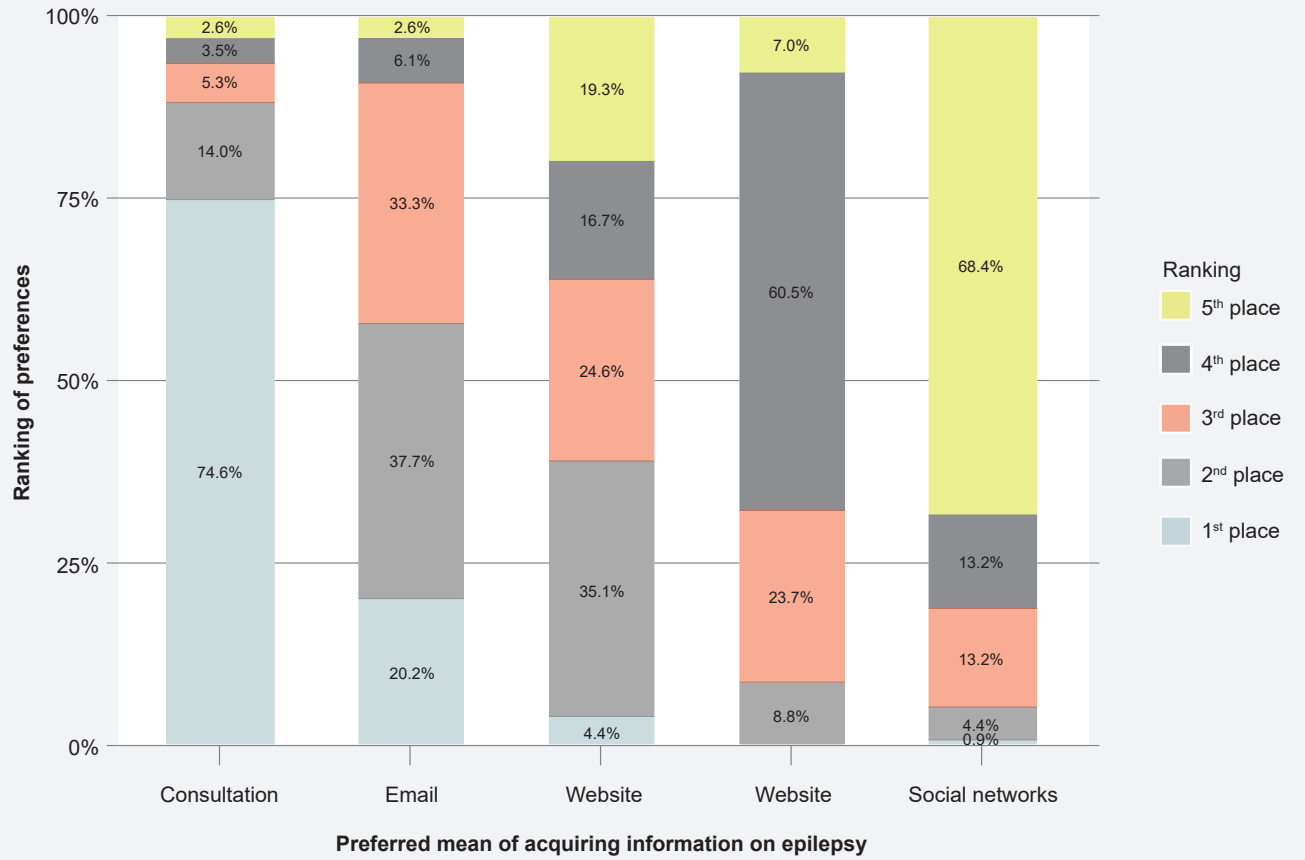


Figure 3 – Preferences of supports for acquiring new knowledge of the disease

To illustrate this, patients who wish to become pregnant and value the importance of breastfeeding can be expected to actively seek information and be more likely to respond to medical inquiries in this area. We can also argue a potential information bias related to the unsupervised methodology of electronically filling in the questionnaire, initially chosen to overcome the restrictions of the Covid pandemic (i.e., patients could access external sources of information). It is worth mentioning that both biases could potentially contribute to an increased accuracy rate, showing suboptimal knowledge of the disease.

In addition to the described biases, this study has several limitations:

- Although five hospitals were involved, a final small group of patients was obtained, reflecting only part of the Portuguese population;
- No patients followed by private neurologists or in primary healthcare were included, with potentially higher economic status, higher education and presenting with controlled conditions. This fact could prevent the generalisation of the results to the whole population of WWE of childbearing age;
- The patients' demographic and clinical characteristics were based on the information provided in the questionnaire (i.e., it was not confirmed through consultation records, for example). This methodological aspect prevents from identifying the characteristics of non-respondents, reducing the control of selection bias;
- The questionnaire that was used, particularly the scale for the assessment of the patient's knowledge of epilepsy, was not validated, a limitation shared by recent previous studies carried out in other countries.[12-14,16]

Further studies will be very useful to confirm and generalise the conclusions, particularly using groups of patients from other regions in Portugal, as well as in other clinical contexts and making an additional effort to validate assessment scales.

## CONCLUSION

Women with epilepsy of childbearing age are a group of patients with special healthcare needs, and their knowledge of the impact of epilepsy on the different domains of

woman's health is crucial for making informed decisions in family planning. Despite the limitations of the study, important gaps were found in the knowledge of Portuguese WWE regarding these issues. Health education aimed at this group of patients should be a concern for medical teams, and the consultation should be prioritised as the adequate setting for patient education.

## AWARDS AND PREVIOUS PRESENTATIONS

The results of the unicentric stage of the study were presented as oral communication to the *Congresso Nacional de Neurologia* of the Portuguese Society of Neurology held in 27-30 October 2021.

## AUTHOR CONTRIBUTION

PLN: Writing and critical revision of the manuscript; study design; statistical analysis; data collection, interpretation, and validity.

RV, ES, JV, MM, BM, JMD: Writing and critical revision of the manuscript; study coordination and implementation at the hospital; data collection, interpretation, and validity at the hospital.

AP, AM, RP, SD, DC, AR: Writing and critical revision of the manuscript; data collection, interpretation, and validity at the hospital

FS, MRS, FA, IM, VBS, SCS, JP, AM: Writing and critical revision of the manuscript; clinical validity of the participants' inclusion at the hospital.

RT: Writing and critical revision of the manuscript; global coordination and study design; formulation of the hypothesis of the study; clinical validity of the participants' inclusion at the hospital; data collection, interpretation and validity.

## HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

## CONFLICTS OF INTEREST

PLN: Financial support by Sanofi to attend the European Academy of Neurology Annual Congress 2022.

ASP: Financial support by Sanofi to attend an international meeting.

MM: Financial support by Roche for the registration at the "Advanced course: Neurodegenerative diseases 2nd edition".

SD: Financial support by Merck, Biogen, and Roche to attend meetings and/or travels.

AR: Financial support by Roche and Boehringer Ingelheim to attend meetings and/or travels.

FS: Received a fee from Bial as speaker in a Tecnifar symposium; received financial support by Bial and Eisai to attend meetings; took part in the Advisory Board of Angelini.

FA: Received a fee from Alter for a presentation.

VBS: Receive a fee for presentations from Bial and Eisai; received a fee as speaker, for writing manuscripts and to attend educational events of Bial and Eisai; received financial support regarding travels from Bial, Eisai, Boehringer Ingelheim, Novartis and Daiichi Sankyo.

JP: Received a fee as a speaker from Bial and Eisai; financial support by Bial, Eisai and Tecnifar to attend meetings.

The remaining authors declare that there were no conflicts of interest in writing this manuscript.

## FINANCIAL SUPPORT

The authors declare that there was no financial support in writing this manuscript.

## REFERENCES

1. Baeta É, Pimentel J, Luzeiro I, Guimarães P. Comissão Epilepsia no Feminino - Vigilância e tratamento da mulher com epilepsia: proposta de normas no âmbito da LPCE. Liga Portuguesa Contra a Epilepsia. 2011. [accessed 2020 Mar 16]. Available from: https://epilepsia.pt/wp-content/uploads/2021/01/comisso-epilepsia-no-feminino_lpce_v1.pdf.
2. Li Y, Meador KJ. Epilepsy and pregnancy. Continuum. 2022;28:34-54.
3. Coulam CB, Annegers JF. Do anticonvulsants reduce the efficacy of oral contraceptives? Epilepsia. 1979;20:519-25.
4. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia. 2013;54:11-27.
5. O'Brien MD, Guillebaud J. Contraception for women taking antiepileptic drugs. J Fam Plann Reprod Health Care. 2010;36:239-42.
6. Harden CL, Meador KJ, Pennell PB, Allen Hauser W, Gronseth GS, French JA, et al. Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes. Epilepsia. 2009;50:1237-46.
7. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;2016:CD010224.
8. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, Mckay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014;2014:CD010236.
9. Harden CL, Hopp J, Ting TY, Pennell PB, French JA, Allen Hauser W, et al. Management issues for women with epilepsy - focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009;50:1229-36.
10. Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure. 2015;28:29-32.
11. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Management issues for women with epilepsy - Focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels,

and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009;50:1247-55.
12. Pack AM, Davis AR, Kritzer J, Yoon A, Camus A. Antiepileptic drugs: are women aware of interactions with oral contraceptives and potential teratogenicity? Epilepsy Behav. 2009;14:640-4.
13. Metcalfe A, Roberts JI, Abdulla F, Wiebe S, Hanson A, Federico P, et al. Patient knowledge about issues related to pregnancy in epilepsy: a cross-sectional study. Epilepsy Behav. 2012;24:65-9.
14. Dierking C, Porschen T, Walter U, Rösche J. Pregnancy-related knowledge of women with epilepsy — an internet-based survey in German-speaking countries. Epilepsy Behav. 2018;79:17-22.
15. McGrath A, Sharpe L, Lah S, Parratt K. Pregnancy-related knowledge and information needs of women with epilepsy: a systematic review. Epilepsy Behav. 2014;31:246-55.
16. Vazquez B, Gibson P, Kustra R. Epilepsy and women's health issues: unmet needs-survey results from women with epilepsy. Epilepsy Behav. 2007;10:163-9.
17. Kochen S. Pregnant women with epilepsy in a developing country. Open Neurol J. 2011;5:63-7.
18. Kampman MT, Johansen SV, Stenvold H, Acharya G. Management of women with epilepsy: are guidelines being followed? Results from case-note reviews and a patient questionnaire. Epilepsia. 2005;46:1286-92.
19. Espinera AR, Gavvala J, Bellinski I, Kennedy J, Macken MP, Narechania A, et al. Counseling by epileptologists affects contraceptive choices of women with epilepsy. Epilepsy Behav. 2016;65:1-6.
20. Abe K, Hamada H, Yamada T, Obata-Yasuoka M, Minakami H, Yoshikawa H. Impact of planning of pregnancy in women with epilepsy on seizure control during pregnancy and on maternal and neonatal outcomes. Seizure. 2014;23:112-6.
21. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. 2018. [accessed 2020 Mar 15]. Available from: https://www.ema.europa.eu/en/documents/press-release/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf.
22. Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia. 2015;56:1006-19.
23. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81:1-13.
24. Hernández-Díaz S, McElrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017;82:457-65.
25. Birnbaum AK, Meador KJ, Karanam A, Brown C, May RC, Gerard EE, et al. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. JAMA Neurol. 2020;77:441-50.
26. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr. 2014;168:729-36.