University of Szeged

Albert Szent-Györgyi Medical School

Doctoral School of Interdisciplinary Medicine

Prevention Related to Reproductive Health

Selected Neuropsychiatric Diseases, Childbearing, Breastfeeding and Choice of Contraception

PhD Thesis

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Abbreviations

AED: Antiepileptic drug

ART: Assisted Reproduction Technology

BMI: Body mass index

CBZ: Carbamazepine

CIS: Clinically isolated syndrome

CNS: Central nervous system

CSF: Cerebrospinal fluid

CT: Computed tomography

CRP: C-reactive protein

DMD: Disease-modifying drugs

EDSS: Expanded Disability Status Scale

ICD-10: International Classification of Diseases Tenth revision

IFN: Interferon

IL: Interleukin

ILAE: International League Against Epilepsy

HLA: Human leukocyte antigen

LARC: Long acting reversible contraception

LAM: lactional amenorrhoe

LEV: Levetiracetam

LTG: Lamotrigine

MCM: Major congenital malformation

MS: Multiple sclerosis

NK: Natural killer cell

MRI: Magnetic resonance imaging

OGP: Oligoclonal gammopathy

PPMS: Primary progressive multiple sclerosis

PRIMS: The Pregnancy in Multiple Sclerosis clinical trial

PRISMS: Prevention of Relapses and Disability by Interferon β-1a clinical trial

PG: Primary generalized epilepsy

PF: Primary focal epilepsy

RRMS: Relapsing-remitting multiple sclerosis

SD: Standard deviation

SG: Secondary generalized epilepsy

SF: Secondary focal epilepsy

SGA: Small for gestational age

SLE: Systemic lupus erythematosus

SPMS: Secondary progressive multiple sclerosis

SPSS: Statistical Package for the Social Sciences

Th: T-helper

TSH: Thyroid stimulating hormone

UV-B: Ultraviolet-B

VPA: Valproic acid

WWE: Women with epilepsy

List of publications related to the subject of the thesis

Paper I.

Vanya M, Nyari T, Bencsik K, Bartfai G. Pregnancy and perinatal outcomes among women with multiple sclerosis: a retrospective case-controlled study in South Hungary. *J Matern Foetal Neonatal Med* 2014 Apr; 27(6):577-581. (SJR indikátor: Q2, IF: 1.367)

Paper II.

Vanya M, Árva-Nagy N, Szili K, Szok D, Bartfai G. Effects of maternal epilepsy and antiepileptic therapy in women during pregnancy. *Ideggyógyászati Szemle* 2015;68(3-4):105-112. (SJR indikátor: Q4, IF: 0.376)

Paper III.

Vanya, M, Devosa, I., Barabás, K., Bártfai, G., & Kozinszky, Z. (2018). Choice of contraception at 6-8 weeks postpartum in south-eastern Hungary. *Eur J Contracept Reprod Health Care*, 23(1), 52-57. doi:10.1080/13625187.2017.1422238 (SJR indikátor: Q2, IF: 1.382)

List of publications not related to the subject of the thesis

Devosa, I., Kozinszky, Z., Vanya, M., Szili, K., Fáyné Dombi, A., & Barabás, K. (2016). [Knowledge of university students in Szeged, Hungary about reliable contraceptive methods and sexually transmitted diseases]. *Orv Hetil, 157*(14), 539-546. doi:10.1556/650.2015.30356

Herczeg, Z., Vanya, M., Szili, K., Dézsi, C., Nagy, Z., & Szabó, J. (2016). [Genetic and epigenetic factors of polycystic ovary syndrome]. *Orv Hetil, 157*(32), 1275-1281. doi:10.1556/650.2016.30434

Kozinszky, Z., Pásztor, N., Vanya, M., Sikovanyecz, J., & Pál, A. (2013). Management of severe idiopathic oligohydramnios: is antepartum transabdominal amnioinfusion really a treatment option? *J Matern Foetal Neonatal Med, 26*(4), 383-387. doi:10.3109/14767058.2012.733753

Szili, K., Szabó, A., Vanya, M., Bártfai, G., & Szabó, J. (2014). [News methods for second trimester screening of Down syndrome: statistical analysis of the use of nasal bone length and prenasal thickness]. *Orv Hetil, 155*(47), 1876-1881. doi:10.1556/OH.2014.29991

Sólya, K., Dézsi, C., Vanya, M., Szabó, J., Sikovanyecz, J., Kozinszky, Z., & Szili, K. (2015). [Clinical aspects of congenital maxillofacial deformities]. *Orv Hetil, 156*(37), 1483-1490. doi:10.1556/650.2015.30240

Vanya, M. (2015). [Outcomes of childbearing and pregnancy in women with multiple sclerosis--a literature review]. *Orv Hetil, 156*(34), 1360-1365. doi:10.1556/650.2015.30222

Vanya, M., & Devosa, I. (2018). Prevalence of psychiatric disorder-related consequences in male prisoners: a cross-sectional study. *Public Health, 154*, 11-13. doi:10.1016/j.puhe.2017.10.001

Vanya, M., Devosa, I., Barabás, K., Bártfai, G., & Kozinszky, Z. (2018). Choice of contraception at 6-8 weeks postpartum in south-eastern Hungary. *Eur J Contracept Reprod Health Care, 23*(1), 52-57. doi:10.1080/13625187.2017.1422238

Vanya, M., Devosa, I., Szok, D., & Bartfai, G. (2016). [Diagnosis and treatment of stroke during pregnancy]. *Neuropsychopharmacol Hung, 18*(3), 143-146.

Vanya, M., Devosa, I., Szok, D., & Bártfai, G. (2016). [Preconceptional and perinatal challenges of pregnancy in women with epilepsy]. *Orv Hetil, 157*(15), 563-568. doi:10.1556/650.2016.30342

Vanya, M., Dezsi, C., Szili, K., Devosa, I., Sipos, O., Nagy Z, Z., Bártfai, G. (2017). [Forensic aspects of sexul assault]. *Psychiatr Hung, 32*(2), 238-245.

Vanya, M., Fejes, I., Jako, M., Tula, A., Terhes, G., Janaky, M., & Bartfai, G. (2015). Lyme disease associated neuroretinitis - Case report. *Acta Microbiol Immunol Hung, 62*(4), 403-408. doi:10.1556/030.62.2015.4.5

Vanya, M., Füvesi, J., Kovács, Z. A., Gorgoraptis, N., Salek-Haddadi, A., Kovács, L., & Bártfai, G. (2016). NMDA-receptor associated encephalitis in a woman with mature cystic ovarian teratoma. *Ideggyogy Sz, 69*(11-12), 427-432. doi:10.18071/isz.69.0427

Vanya, M., Jakó, M., Terhes, G., Szakács, L., Kaiser, L., Deák, J., & Bártfai, G. (2016). [Low rate of oropharyngeal human papillomavirus infection among women with cervical lesion. Preliminary results from the South-Eastern Hungarian population]. *Orv Hetil, 157*(2), 70-73. doi:10.1556/650.2015.30321

Vanya, M., Matuz, M., Benko, R., Viola, R., Horvath-Sziklai, A., Soos, G., & Bartfai, G. (2017). Knowledge and opinion of pharmacists on emergency contraceptive pills in Hungary. *Int J Clin Pharm, 39*(3), 594-600. doi:10.1007/s11096-017-0448-0

Vanya, M., Szili, K., Devosa, I., & Bártfai, G. (2015). [Risk of maternal and foetal disease among women older than 40 years]. *Orv Hetil, 156*(49), 1987-1990. doi:10.1556/650.2015.30286

Vanya, M., Szili, K., Zámolyi, S., Magyar, H., Kőrösi, G., Benkő, Á., . . . György, L. (2015). [Differential diagnostic and therapeutic aspects of Q-fever in a male prisoner. Case report]. *Orv Hetil, 156*(18), 741-743. doi:10.1556/OH.2015.30098

Vanya, M., Szucs, S., Vetro, A., & Bartfai, G. (2017). The potential role of oxytocin and perinatal factors in the pathogenesis of autism spectrum disorders - review of the literature. *Psychiatry Res, 247*, 288-290. doi:10.1016/j.psychres.2016.12.007

Vanya, M., Szücs, S., Szili, K., Vetró, Á., & Bártfai, G. (2015). [The possibility of prenatal diagnosis of autism spectrum disorder]. *Psychiatr Hung, 30*(3), 303-307.

INTRODUCTION

Neuropsychiatric diseases substantially influence reproductive health, pregnancy outcomes, and foetal development, posing a significant interdisciplinary challenge in both clinical care and research. Among these conditions, Multiple Sclerosis (MS) and Epilepsy represent major concerns due to their potential to adversely affect both maternal and foetal health. In affected individuals of reproductive age, particularly women, the importance of informed reproductive planning—including the selection and consistent use of adequate contraceptive methods—cannot be overstated.

Multiple Sclerosis predominantly affects women of reproductive age, making pregnancy management an important clinical concern. MS is characterized by unpredictable disease progression, exacerbations, and remissions, which complicate both pregnancy management and decision-making related to disease-modifying treatments. Current evidence suggests that pregnancy exerts a stabilizing effect on MS, with decreased relapse rates particularly during the third trimester, but an increased relapse risk postpartum. Nevertheless, understanding and mitigating the risks associated with MS-related complications, such as miscarriage and intrauterine foetal death, remain challenging.

Epilepsy introduces unique complexities due to potential adverse effects of antiepileptic drugs (AEDs) on pregnancy outcomes, congenital malformations, and neonatal neurodevelopment. Despite advances in therapeutic options, pregnancy in women with epilepsy (WWE) requires personalized clinical strategies. Selection of AED therapy must effectively balance maternal seizure control and foetal safety, necessitating careful monitoring and dose adjustments throughout pregnancy, particularly during physiological changes that alter drug metabolism.

Further clarification of these associations could facilitate targeted preventive strategies and early intervention programs, thereby improving long-term developmental outcomes for at-risk children.

I. Multiple sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). It is one of the most common causes of disability in young adults, affecting

approximately 1 in 1000 individuals in Western countries, with about 2.5 million people affected worldwide (1, 2). In Hungary, the prevalence is 65 per 100,000 persons (3, 4).

I/1. Clinical subtypes of MS

The relapsing-remitting form of MS (RRMS) affects approximately 85% of patients and is characterized by relapses of neurological dysfunction followed by periods of remission (5, 6). Within 25 years, most patients with RRMS (around 90%) transition into secondary progressive MS (SPMS), characterized by progressive neurological disability without distinct remissions (7, 8). A primary progressive form of MS (PPMS) affects around 15% of patients, featuring a steady decline in neurological function without clear remissions. Some patients with PPMS may also experience acute clinical relapses superimposed on a continuous functional decline (7, 8). Despite varying clinical patterns and progression rates, MS is considered one disease with multiple clinical phenotypes (9, 10).

I/2. Pathophysiology of MS

MS is characterized by inflammation, demyelination, and axonal degeneration, either primary or secondary (9, 10). Oligodendrocytes, responsible for synthesizing and maintaining the myelin sheath of axons in the CNS, are the primary targets of immune attacks. These attacks predominantly involve T-cells and activated macrophages or microglia (11, 12). Two distinct pathological features are observed in the CNS: focal demyelinated plaques and diffuse global brain injury. Early in the disease, demyelinated plaques, characterized by primary demyelination and astrocytic scarring, dominate. Over time, progressive diffuse brain injury develops through cumulative inflammation, leading to diffuse tissue damage and brain atrophy. Eventually, chronic multifocal sclerotic plaques form (13, 14). The median time from disease onset to the necessity of a walking aid is about 20 years (15–18). Life expectancy in MS patients is approximately 10 years shorter compared to the general population (19, 20).

I/3. Etiology of MS

MS is considered an immune-mediated disorder arising from complex interactions between genetic and environmental factors (21–24). Candidate gene studies have identified an

association between MS and the human leukocyte antigen (HLA)-DRB1*1501 (6p21), confirmed through large genetic linkage studies in Northern European families (25–27).
Environmental susceptibility factors for developing MS have been supported by migration studies. Migrating from low- to high-incidence areas before age 15 significantly increases MS risk compared to migration after age 15 (28–31). Epstein-Barr virus (EBV), a member of the herpes virus family, is notably associated with increased MS risk; individuals with childhood EBV infection have approximately a 10-fold greater risk, while those experiencing mononucleosis have at least a 20-fold higher risk compared to uninfected individuals (32–35). Furthermore, the prevalence of MS increases with geographic latitude worldwide. Although this difference has recently begun diminishing, reduced sunlight exposure (UV-B radiation) and corresponding decreases in vitamin D synthesis remain proposed influences on MS risk (36–43).

I/4. Diagnosis of MS

There is no pathognomonic test for MS; diagnosis primarily relies on patient history. Due to the inflammatory process, MS symptoms typically emerge subacutely over hours to days, lasting from more than 24 hours up to 4–6 weeks, followed by full or partial remission. Historically, MS diagnosis has depended on clinical evidence of dissemination in time (≥2 attacks) and space (≥2 CNS lesions). However, since the introduction of the Poser criteria in 1983 (44, 45), clinical and paraclinical investigations—including MRI, visual evoked potentials, and cerebrospinal fluid (CSF) analyses for oligoclonal bands—have supplemented clinical diagnosis. Updated diagnostic criteria known as the McDonald criteria were introduced in 2001 and revised in 2011 (46–51), emphasizing MRI evidence of dissemination in space and time. Differential diagnoses for MS include acute disseminated encephalomyelitis, CNS infections, systemic lupus erythematosus (SLE), sarcoidosis, neuromyelitis optica, and CNS manifestations of malignancies in younger patients (52, 53).

I/5. Amelioration of MS during pregnancy

Clinical fluctuations related to hormonal changes during menstrual cycles, pregnancy, and sex hormone treatments have been reported in MS and other autoimmune diseases (54–56). Various immunologically active substances in the serum of pregnant women possess anti-inflammatory and immunosuppressive effects, potentially influencing MS (57, 58). Experimental allergic

encephalomyelitis models demonstrate that both estrogen and progesterone can suppress disease activity. An increased postpartum risk of autoimmune flares might result from reduced estrogen-mediated immune modulation, supported by evidence from MRI studies evaluating oral estriol treatment effects on MS (59).

Suppression mechanisms by sex hormones likely include inhibition of nitric oxide production in microglia and reduced synthesis of pro-inflammatory factors. Pregnancy-associated proteins such as alpha-fetoprotein and interleukin-10 (IL-10) further down-regulate cellular immunity (60, 61). MS pathogenesis predominantly involves T-helper type 1 (Th1)-mediated immune responses, which are counteracted by a Th2-dominant state during pregnancy, reducing disease activity. Postpartum shifts back to Th1 dominance partially explain the increased relapse risk in the initial 3–6 months after delivery (62–73). Regulatory T-cells and natural killer (NK) cells also play roles in this complex immune modulation during pregnancy, though precise mechanisms remain unclear.

I/6. Effects of MS on pregnancy, delivery, and birth outcomes

Epidemiological studies demonstrate that MS frequently manifests postpartum among women of reproductive age. Recent research has emphasized pregnancy's influence on MS disease course, particularly postpartum relapse rates, driven mainly by Th1 cells and pro-inflammatory cytokines crossing the blood-brain barrier and causing inflammation (74, 75). Elevated estrogen levels during pregnancy temporarily promote Th2 cytokine dominance, stabilizing MS and decreasing relapse frequency, especially in the third trimester. Postpartum cytokine fluctuations subsequently trigger disease relapses.

Saraste et al. reported reduced NK cell levels among women receiving postpartum disease-modifying medication, correlating with lower relapse rates relative to untreated women. Post-delivery relapse rates range from 25–50%, highest within the first three months postpartum.

With the advent of disease-modifying therapies (DMTs), questions have arisen about optimal therapy discontinuation timing during pregnancy and potential long-term impacts on conception, pregnancy outcomes, delivery circumstances, and neonatal health. Although studies on beta-interferon and glatiramer acetate remain preliminary and somewhat controversial, current evidence generally suggests no negative impact of these treatments on foetal development or pregnancy outcomes (76–81).

II. Epilepsy and pregnancy and perinatal outcomes

II/1. Epidemiology of epilepsy

Epilepsy is a common neurological disorder, with an estimated prevalence in the European Union of approximately 0.5–0.7%. Among pregnant women, the prevalence has been estimated at 0.3–0.5% (82, 83). The range of etiological and risk factors for epilepsy varies according to age and geographical location. Congenital, developmental, and genetic factors are most commonly associated with epilepsy in childhood, adolescence, and early adulthood. Head trauma, CNS infections, and tumors may occur at any age and can lead to symptomatic epilepsy.

II/2. Diagnosis of epilepsy

Successful identification of etiological or risk factors depends on the thoroughness and standardization of investigations. Without clear methodological standards, evaluating study results becomes challenging (84–86). According to the International League Against Epilepsy (ILAE) classification, epilepsy can be classified as primary (idiopathic) or secondary (symptomatic). Idiopathic epilepsy specifically refers to genetically determined epilepsy syndromes with well-defined clinical and EEG characteristics. However, it is frequently used more broadly to describe epilepsies with unknown etiology. The classification of epilepsy syndromes (primary or secondary) and seizure types (focal or generalized) should follow the revised ILAE classification (87).

II/3. Use of antiepileptic drugs (AEDs) during pregnancy

Management of women with epilepsy (WWE) should focus on optimizing treatment well before conception. This involves close collaboration between neurologists and obstetrician-gynecologists, selecting the AED most likely to control seizures at the lowest effective dose, avoiding valproic acid (VPA) when suitable alternatives exist, minimizing polytherapy, providing dietary supplementation with folic acid, and offering pre-conception counseling (88–91). Discontinuation of pharmacological therapy is generally not feasible, as seizures during pregnancy may pose greater risks to both mother and fetus than treatment (88–91).

Recent studies have identified AED use during pregnancy as a major cause of congenital malformations (MCMs) and potential negative effects on cognitive development in infants following prenatal exposure (87, 92, 93). Although some studies hypothesize that maternal epilepsy itself may contribute to MCMs (94–98), recent evidence suggests that AED therapy is the primary cause of malformations (87, 92, 93). Numerous studies have evaluated the relationship between MCM rates and long-term effects of maternal AED exposure. A summary of teratogenic risks associated with various AEDs is presented in Supplement 1 (see in Appendix) (99).

The risk of MCMs significantly increases in infants exposed to AEDs during the first trimester, and this risk rises further with polytherapy (100). The teratogenic effect of AEDs is dose-dependent and influenced by additional factors (101, 102). The highest risk is associated with high-dose valproic acid compared to other AEDs such as carbamazepine, phenytoin, and lamotrigine (103). Few studies have clearly separated the effects of epilepsy itself from AED exposure regarding MCM and other pregnancy outcomes. Nevertheless, several studies suggest an approximately threefold increased risk of MCMs among children born to WWE compared to children of healthy women (104–111). Periconceptional dietary supplementation with folic acid significantly reduces the risk of congenital malformations, particularly anencephaly and spina bifida (91).

II/4. Breastfeeding and AEDs

Breastfeeding has known benefits, yet concerns remain about its safety during AED therapy due to potential cognitive impacts on infants. Pamela Crawford’s review (112, 113) recommends encouraging WWE to breastfeed. The concentrations of various AEDs in breast milk typically parallel maternal plasma concentrations. The total quantity of AEDs transferred via breast milk is generally much lower than transplacental transfer during pregnancy.

However, since the elimination mechanisms for AEDs are not fully developed in early infancy, repeated exposure through breast milk might result in drug accumulation (114). A prospective multicenter study with extensive data indicated persistent adverse cognitive effects in children up to six years following foetal VPA exposure (115, 116).

II/5. Seizures in WWE during pregnancy and perinatal outcomes

Recent studies indicate that about 90% of WWE experience successful pregnancy outcomes and deliver healthy children without increased obstetric or neonatal complications (117–120). However, earlier publications reported increased risks of miscarriage, preterm birth, intrauterine growth restriction, and low birth weight among neonates of WWE (121, 122). Additionally, higher rates of maternal complications, including gestational diabetes mellitus, hypertensive disorders, and intracranial antepartum hemorrhage, have been reported (123–126). A major concern for WWE is the potential influence of pregnancy on seizure frequency. The EURAP study found that nearly 60% of WWE remained seizure-free during pregnancy (127, 128). Seizure patterns during pregnancy may be affected by fluctuating estrogen and progesterone levels (129, 130). Serum AED concentrations and metabolic changes (such as diabetes mellitus) are also significant influencing factors (131).

III. Choice of contraception

III/1. Long-acting reversible contraception (LARC)

In 2015, Hungary's total fertility rate was 1.45, slightly below the European Union average (132). While Hungarian women generally plan to have around 2.4 children, the majority ultimately have only one, influenced by factors such as career aspirations, financial constraints, and family circumstances (133). Additionally, in 2016, approximately 20% of live births were followed by induced abortion (130). A prevailing trend toward delayed childbearing presents challenges for contraceptive care, as older women face increased risks with certain methods, such as combined hormonal contraception, and often have reduced access to effective options (134). Reproductive intentions and sexual behaviour tend to evolve with age. Long-acting reversible contraception (LARC) is widely recognised as a suitable postpartum method, yet its utilization in Hungary remains extremely low, around 5.9%. Ensuring timely and effective contraception in the postpartum period—particularly within the first 6–8 weeks after birth—is essential, especially among high-risk populations.

III/2. Lactational amenorrhoea (LAM)

Lactational amenorrhoea (LAM), which results from the suppression of ovulation through exclusive breastfeeding, can serve as a reliable contraceptive method during the early postpartum phase. Women should be counselled on the immediate postpartum use of effective methods such as intrauterine devices (IUDs), levonorgestrel-releasing intrauterine systems (LNG-IUS), and progestogen-only subdermal implants (137). Contraceptive methods should ideally be initiated within 21 days of delivery, regardless of breastfeeding status. Understanding the determinants of effective contraceptive use during the puerperium can assist public health professionals in identifying vulnerable groups and developing targeted educational interventions to promote uptake of modern hormonal contraception in the postpartum population (138,140).

Our study aimed to examine how sociodemographic factors, economic status, sexual and contraceptive history, and breastfeeding practices influence postpartum contraceptive use, with a particular focus on the adoption of highly effective methods or reliance on LAM (141,142,143).

AIMS OF THE THESIS

The objectives of the present thesis were to investigate:

I. The effects of multiple sclerosis on pregnancy, delivery, and neonatal outcomes (Paper I).
II. The impact of epilepsy on pregnancy, delivery, and neonatal parameters (Paper II).
III. Contraceptive choices (Paper III.)

This thesis aims to comprehensively explore these complex interactions. By systematically investigating clinical outcomes, medication impacts, and potential risk factors associated with these neuropsychiatric conditions with a particular emphasis on the role of adequate contraception in mitigating avoidable risks, this research provides valuable insights for optimizing the care of affected pregnant women and their offspring. Enhanced interdisciplinary cooperation and informed clinical decision-making are essential to effectively manage the delicate balance between maternal health and foetal safety.

MATERIALS AND METHODS

Multiple sclerosis (MS)

All pregnant women (n=102) diagnosed with relapsing-remitting multiple sclerosis (RRMS), who received obstetric care at the Department of Obstetrics and Gynecology and neurological treatment at the Department of Neurology, University of Szeged, between January 1, 1998, and December 31, 2012, were enrolled in this study. Out of these 102 RRMS patients, 65 were treatment-naive for disease-modifying drugs (DMD). Since it is known that DMD treatment can predispose pregnant women to early pregnancy and neonatal complications, patients requiring DMD due to symptom progression were excluded. The control group, selected by simple randomization, consisted of 65 age-matched pregnant women without MS or any other neuroimmunological disorders. Both the case and control groups were further divided into primigravida and multigravida subgroups.

Epilepsy

This retrospective case-control study included all pregnant women with epilepsy (n=91) who were managed at the Department of Obstetrics and Gynecology and the Department of Neurology, University of Szeged, between December 31, 2000, and March 31, 2014. Women with epilepsy (WWE) were divided into three groups: AED-treatment-naive, monotherapy, and polytherapy. Controls (n=182) were randomly selected from pregnant women without epilepsy or other neuropsychiatric disorders, who delivered at our tertiary care center during the same period. Control participants were referred from the Department of Obstetrics and Gynecology to the Department of Neurology for a neurological evaluation.

Contraception

A total of 1,875 women were initially invited to participate in the study, of whom 611 declined to provide consent. Participants were excluded if they were under the age of 18 (n = 16), illiterate (n = 2), or non-Hungarian speakers (n = 3).

Among the eligible participants, those with access to email (n = 1,517) received a secure link to an online questionnaire during the 6th to 8th weeks postpartum. Participants without email

access (n = 62) were sent the questionnaire via standard postal mail. Two follow-up reminders were issued to non-respondents at approximately one and two weeks after the initial contact. Despite these efforts, 336 women did not complete the questionnaire, resulting in an overall response rate of 67%. Additionally, 644 respondents were excluded from the analysis as they had not resumed sexual activity at the time of data collection. The final analytical sample consisted of 599 women who completed the questionnaire.

Patient Characteristics

Sociodemographic data, including highest educational level, marital status, employment status, and residence of participants, were analyzed.

Obstetric Data

The mode of delivery and pregnancy-related complications were assessed. Additional parameters evaluated included maternal age, gravidity, parity, maternal medical and obstetric histories, pregnancy outcomes, and neonatal outcomes such as gestational age at delivery, prematurity, postmaturity, intrauterine growth restriction, minor or major congenital malformations, and maternal or perinatal complications. Neonatal parameters analyzed were birth weight, birth length, head and chest circumference, and breastfeeding rates within the first 6 months.

MS-related Data

Clinical subtype and disease duration of MS were analyzed. Disability levels were measured using the Expanded Disability Status Scale (EDSS).

Epilepsy-related Data

Epilepsy-related data included AED therapy details (indication, dosage, timing), exposure to epileptic seizures during the first trimester of pregnancy, and potentially AED-related congenital malformations. Epilepsy syndromes (primary or secondary) and seizure types (focal or generalized) were classified according to the revised ILAE classification (2010).

The primary endpoint was the rate of major congenital malformations. Secondary endpoints included rates of spontaneous abortion, preterm birth, neonatal birth weight, birth length, and head and chest circumferences.

Contraception-related Data

To identify predictors of effective postpartum contraceptive use—including lactational amenorrhoea (LAM), either alone or in combination with other methods such as hormonal contraception, intrauterine devices, or sterilisation—a binary logistic regression model was employed. All predictor variables were adjusted for maternal age.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 20. For comparison of categorical data, the χ^2 test, Fisher's exact test, and odds ratios (OR) with 95% confidence intervals (CI) were calculated. The independent-samples Student's t-test was applied to compare means. Results were considered statistically significant if $p < 0.05$. Univariate analyses were performed using analysis of variance (ANOVA) for continuous variables and the chi-square (χ^2) test for categorical variables. The logistic regression model was developed using a stepwise approach, with attention to identifying and managing collinearity and potential confounders to improve model robustness. The relationship between predictors and the log-odds of the outcome variable was statistically significant. A p-value of less than 0.05 (two-sided) was considered indicative of statistical significance.

Ethical Approval

The studies were approved by the Regional Ethics Committee of the University of Szeged and complied fully with the Declaration of Helsinki (1961).

Approval numbers:

- MS: 194/2010
- Epilepsy: 3136/2012
- Contraception: 125/2011

RESULTS

I. Multiple Sclerosis (MS)

Between 2000 and 2012, 102 pregnancies in women with multiple sclerosis (MS) were observed at our tertiary care centre. Of these, 65 women were treatment-naive with respect to disease-modifying drug (DMD) therapy.

Maternal and neonatal characteristics, as well as the presence of comorbidities in the MS and non-MS groups, are presented in Tables 1, 2 and 3.

General Demographics

The average age at MS diagnosis was 26.37 ± 6.34 years for primigravidas and 27.72 ± 3.9 years for multigravidas. The average age at first pregnancy was 29.65 ± 4.49 years for primigravidas and 25.1 ± 4.46 years for multigravidas ($p > 0.05$). The mean Expanded Disability Status Scale (EDSS) score was slightly higher in primigravida women with MS than in multigravidas (1.36 ± 1.2 vs. 1.48 ± 4.4), but the difference was not statistically significant ($p > 0.05$).

The proportion of married women was significantly lower in the control group than in the MS group (34.3% vs. 72.3%, $p < 0.001$). The distribution of MS mothers living in urban and rural areas was similar (46.15% vs. 53.85%, $p > 0.05$). No significant differences were found between the two groups in terms of educational level or employment status. The groups also did not differ statistically regarding other examined parameters.

Table 1. Educational characteristic in the MS case and control groups

	Case group n=63*		**Control group n=65**		**p**
	n	%	n	%	
	Educational level				
Primary school	3	4.62	6	9.23	N.S.
Secondary school	48	73.85	52	80	N.S.
Tertiary school	14	21.54	7	10.77	N.S.

* Missing data in 2 cases.

N.S.: not statistically significant.
Statistical analysis was performed with the chi-square test and Fischer exact test.

Table 2. Maternal socio-demographic characteristic in the MS case and control groups

	Case group n=63*		Control group n=65		p
	n	%	n	%	
Educational level					
Primary school	3	4.62	6	9.23	N.S.
Secondary school	48	73.85	52	80	N.S.
Tertiary school	14	21.54	7	10.77	N.S.
Marital status					
Married	47	72.3	19	34.3	<0.001
Single	9	13.85	31	47.05	N.S.
Divorced	7	10.77	14	15.68	N.S.
Widow	0	0.	1	2.94	N.S.
Employment status					
Employed	45	69.23	40	61.54	N.S.
Unemployed	20	30.77	25	38.46	N.S.
Residency					
Urban	30	46.15	24	36.92	N.S.
Rural	35	53.85	41	63.07	N.S.

* Missing data in 2 cases.
N.S.: not statistically significant.
Statistical analysis was performed with the chi-square test and Fischer exact test.

Table 3. Maternal accompying disorders in women with MS

Prevalence of accompying disorders					
	Cases (n=65)		**Controls (n=65)**		p
	n	%	n	%	
Gestational diabetes mellitus					
Yes	**3**	**4.62**	**11**	16.92	0.018*
No	**62**	**95.38**	**54**	83.08	
Total	**65**	**—**	**65**	—	
Essential hypertension					
Yes	**4**	**6.15**	**5**	7.69	N.S.
No	**61**	**93.85**	**60**	92.31	
Total	**65**	**—**	**65**	—	
Depressive disorders					
Yes	**12**	**18.46**	**0**	0	<0.001**
No	**53**	**81.54**	**65**	100	
Total	**65**	**—**	**65**	—	
Hyperthyroidism					
Yes	1	1.54	0	0	N.S.
No	64	98.46	65	100	
Total	65	—	65	—	

p: level of significance <0.05
N.S.: not statistically significant.
Statistical analysis was performed with the chi-square test and Fischer exact test.

Hospitalization for more than five days occurred in 33.85% of women with MS, compared to none in the control group ($p = 0.004$). However, this difference was not observed between

primigravida and multigravida subgroups. This finding is associated with MS and MS-related depressive disorders ($p < 0.001$); the affected women were treated with antidepressants.

Twenty-five women (38.46%) had experienced at least one pregnancy before being diagnosed with MS. The prevalence of vaginal delivery was significantly lower ($p = 0.042$) in women whose pregnancies occurred before their MS diagnosis (Table 4).

Miscarriages and intrauterine foetal deaths were significantly more frequent in the MS group compared to the non-MS control group ($p < 0.001$ and $p = 0.035$, respectively). Twelve women in the MS group experienced miscarriages between the 6th and 13th gestational weeks, and there were eight cases of intrauterine foetal death. Miscarriages were significantly more common among multigravida women with MS than among primigravidas ($p = 0.003$), while intrauterine foetal death was not significantly more frequent in primigravidas ($p = 0.008$).

Table 4. Comparison of delivery mode in the case and control groups in MS

	Women with MS (n=65)		**Women without MS (n=65)**		**p**
	n	%	n	%	
Vaginal delivery	**30**	**46.15**	**40**	**56.92**	**N.S.**
Caesarean section	**18**	**27.69**	**25**	**38.46**	**N.S.**
Miscarriage	**12**	**18.46**	**0**	**0**	**<0.001**
Intrauterine death	**5**	**7.69**	**0**	**0**	**0.035**

N.S.: not statistically significant.
Statistical analysis was performed with the chi-square test Fischer exact test.

Macrosomia and post-term birth rates were similar across both the MS and control subgroups. The average birth weight was 2759 ± 1135 grams in the primigravida MS subgroup, 3221.5 ± 620.8 grams in the multigravida MS subgroup, 2997 ± 831 grams in the primigravida control subgroup, and 3250 ± 561 grams in the multigravida control subgroup. These differences were not statistically significant (Table 5).

Table 5. Comparison of perinatal parameters in the case and control groups in MS

	Women with MS (n=65)		**Women without MS (n=65)**		**p**
	n	%	n	%	
Average birth weight (mean ± SD) (grams)	**3004 ± 904.27**		**3365 ± 552.75**		***N.S.**
Prematurity (< 37 gestational weeks) **< 2500 g** **< 1500 g**	**3** **2** **1**	**4.61** **3.07** **1.54**	**8** **8** **0**	**12.3** **12.3** **0**	**N.S.**
Hospitalization for more than 5 days	**22**	**33.85**	**8**	**12.3**	**0.004**
Small for gestational age	**3**	**4.61**	**0**	**0**	**0.095**
Twin pregnancy	**3**	**4.61**	**0**	**0**	**0.095**

N.S.: not statistically significant.
SD: standard deviation
Statistical analysis was performed with the chi-square test Fischer exact test and
*independent sample t-test.

Other perinatal outcomes—such as prematurity, macrosomia, and post-term birth—did not differ significantly between the MS and control groups.

There were three spontaneous twin pregnancies in the MS group (4.61%), which is higher than the rate of multiple pregnancies in the control group ($p = 0.095$). No multiple pregnancies occurred in the control group. Data on the mode of delivery and neonatal outcomes in the MS and non-MS groups are presented in Table 34 and Table 5.

Other examined variables—including average birth weight, prematurity, small-for-gestational-age status, vaginal delivery, and congenital malformations—also did not differ significantly between the MS group and the matched control group. Prematurity (<37 weeks or <2500 g), post-term birth (>40 weeks), macrosomia (>4500 g), and congenital malformation rates were comparable in both groups. No significant differences were observed in the rate of caesarean section between primigravida and multigravida women with or without MS. However, the rate of vaginal delivery was significantly higher in the control group ($p < 0.001$). Average foetal weight, as well as the rates of prematurity and congenital malformations, were similar in both groups.

Only one newborn required admission to a neonatal intensive care unit due to prematurity (birth weight: 1120 grams).

For personal reasons, 27 women opted for elective termination of pregnancy during the first trimester. One medically indicated termination was performed due to progression of MS symptoms. Two cases of secondary infertility were recorded in both the primigravida and multigravida MS subgroups; all four women were treated with assisted reproductive technology (ART). No significant differences in ART use were observed between the two subgroups (Table 6 and Table 7).

Table 6. Comparison of pregnancy outcomes and mode of delivery in primigravidas and multigravidas women with and without MS

	Primigravidas case group (n=40)		**Multigravidas case group (n=25)**		**Primigravidas control group (n=40)**		**Multigravidas control group (n=25)**		**p-value**
	n	%	n	%	n	%	n	%	
Miscarriage	**3**	**7.5**	**9**	**36**	**0**	**0**	**0**	**0**	0.003
Intrauterine death	**5**	**12.5**	**0**	**0**	**0**	**0**	**0**	**0**	N.S.
Caesarean section	**9**	**22.5**	**5**	**20**	**9**	**22.5**	**16**	**64**	N.S.
Vaginal delivery	**23**	**57.5**	**11**	**44**	**31**	**77.5**	**9**	**36**	<0.001
Hospitalization for more than 5 days	**15**	**37.5**	**7**	**28**	**0**	**0**	**0**	**0**	N.S.

N.S.: not statistically significant.

Statistical analysis was performed with the chi-square test and Fischer exact test.

T

able 7. Comparison of pregnancy complications in primigravidas and multigravidas women with and without MS

	Primigravidas case group (n=40)		Multigravidas case group (n=25)		Primigravidas as control group (n=40)		Multigravidas as control group (n=25)		p
	n	%	n	%	n	%	n	%	
Average birth weight (g) (mean ± SD)	**2759 ± 1135**		**3221.5 ± 620.8**		**2997 ± 831**		**3250 ± 561**		**N.S.**
Prematurity (<37. gestational weeks; <2500 g)	**1**	**2.5**	**2**	**8**	**5**	**12.5**	**6**	**24**	**N.S.**
Macrosomia (>4500 g)	**0**	**0**	**1**	**4**	**0**	**0**	**3**	**12**	**N.S.**
NICU admission	**1**	**2.5**	**0**	**0**	**0**	**0**	**0**	**0**	**N.S.**

N.S.: not statistically significant
SD: standard deviation
NICU: Neonatal Intensive Care Unit
Statistical analysis was performed with the chi-square test and Fischer exact test.

II. Epilepsy

Maternal characteristics

The mean maternal age at delivery was similar in the epileptic and non-epileptic groups: 29.4 ± 5.26 years vs. 29.66 ± 8.52 years.

Maternal characteristics and comorbidity data for both groups are summarized in Table 8.

The number of obese women was significantly higher in the control group than in the epileptic group (0% vs. 12.64%, $p < 0.001$). Pre-existing hypertension and pre-eclampsia were more prevalent among women with epilepsy (7.69% and 4.4%, respectively) compared to those without epilepsy (0% in both cases; $p < 0.001$ and $p = 0.012$, respectively). There was no significant difference in the prevalence of gestational diabetes mellitus (GDM) between the two groups.

Table 8. Prevalence of concomitant diseases in the WWE and in the control groups

	Women with epilepsy (n=91)		Women without epilepsy (n=182)		p
	n	%	n	%	
Obesity (BMI > 30)	0	0	23	12.64	<0.001
Pre-eclampsia	4	4.4	0	0	<0.012
Hypertension in the medical anamnesis	7	7.69	0	0	<0.001
Gestational diabetes mellitus	5	5.81	6	3.3	N.S.

N.S.: not statistically significant.
BMI: body mass index
Statistical analysis was performed with the chi-square test and Fischer exact test.

Seizures During Pregnancy and the Postpartum Period

The characteristics of maternal seizures are summarized in Tables 9 and 10. Thirty-four women with epilepsy (WWE; 37.36%) did not experience seizures during pregnancy. In contrast, seizures occurred in 57 cases (65.64%) during the gestational period: 26.32% (n = 15) in the first trimester, 24.56% (n = 14) in the second trimester, and 49.12% (n = 28) in the third trimester.

Seizures were also reported at the time of delivery in five cases (8.77%) and during the postpartum period in four cases (7.02%). Three distinct peaks of seizure activity were observed during pregnancy.

The majority of WWE (69.23%, n = 63) did not show changes in seizure frequency. However, 19 women (20.88%) experienced progression of secondary focal seizures. Additionally, five women (5.49%) had generalized tonic-clonic (grand mal) seizures during delivery (Table 9). Changes in seizure pattern were noted in four WWE (4.39%).

Table 9. Seizure occurrence during antepartum and postpartum period in WWE

	WWE (n=91)
No seizures	34/91 (37.36%)
Number of seizures in antepartum period	57/91 (62.64%)
1st trimester	15/91 (16.48%)
2nd trimester	14/91 (15.38%)

3rd trimester	**28/91 (30.77%)**
Number of seizures in the postpartum period	**8/91 (8.79%)**

WWE: women with epilepsy

Table 10. Seizure pattern during pregnancy, at delivery and during puerperium in WWE

	WWE (n=91)	%
No changes in seizure pattern	**63**	**69.23**
Increasing the number of seizures in the 3rd trimester	**19**	**20.88**
Increasing the number of seizures at delivery	**5**	**5.49**
Increasing the number of seizures in the puerperium	**4**	**4.39**

Perinatal Outcomes

The mean gestational age was similar in the non-epileptic group and the epileptic cohort (38.97 ± 2.17 vs. 38.45 ± 2.17 weeks, $p > 0.05$).

A significant difference was observed in the mean birth weight of neonates: 2973.33 ± 960.02 grams in the epileptic group versus 3242.74 ± 582.72 grams in the control group ($p = 0.003$).

The miscarriage rate was higher among women with epilepsy than in the non-epileptic group (7% vs. 0%, $p = 0.001$). The prevalence of vaginal (per vias naturales) delivery was significantly lower among women with epilepsy than among those without epilepsy (53.58% vs. 65.93%, $p = 0.001$). The caesarean section rate was also significantly higher in the epileptic group compared to controls (45.05% vs. 34.06%, $p = 0.022$).

The rates of prematurity and intrauterine growth restriction were similar between the two groups. However, foetal chest circumference and mean birth length were significantly different ($p < 0.001$ for both). Likewise, a significant difference was observed in head circumference between the two groups ($p < 0.001$).

Data on mode of delivery and neonatal parameters are presented in Tables 11 and 12.

Table 11. Comparison of delivery mode and neonatal parameters in WWE and non-WWE
N.S.: not statistically significant.

	WWE (n=91)		non-WWE (n=182)		p
	n	%	n	%	
Vaginal delivery	**50**	**54.94**	**120**	**65.93**	**0.001**
Caesarean section	**41**	**45.05**	**62**	**34.06**	**0.022**
Previous miscarriage	**6**	**6.59**	**0**	**0**	**0.001**
Post-term birth	**21**	**23.07**	**118**	**64.84**	**<0.001**
Mean gestational age (weeks)	**38.97 ± 2.17**		**38.45 ± 2.17**		**N.S**
Prematurity (<37 weeks, <2500 g)	**13**	**14.29**	**20**	**10.98**	**N.S.**
Intrauterine growth restriction	**5**	**5.49**	**3**	**1.65**	**N.S.**

WWE: women with epilepsy
Statistical analysis was performed chi-square test and Fischer exact test.

Table 12. Parameters of neonates of WWE and non-WWE

	WWE (n=91)	non-WWE (n=182)	p
Chest circumference of the newborn (cm)	**32 ± 4.17**	**33 ± 1.08**	**<0.001**
Head circumference of the newborn (cm)	**33.09 ± 4.03**	**33.75 ± 1.26**	**<0.001**
Mean birth length (cm)	**48.93 ± 2.55**	**49.61 ± 3.96**	**<0.001**
Umbilical cord blood pH	**7.28 ± 0.87**	**7.28 ± 0.87**	**N.S**
Mean neonatal birth weight (gram)	**3185.72 ± 550.92**	**3242.74 ± 582.72**	**N.S**
1 minute Apgar score	**8.69 ± 2.04**	**9.75 ± 0.66**	**<0.001**
5 minute Apgar score	**9.64 ± 0.78**	**9.89 ± 0.41**	**<0.001**
10 minute Apgar score	**10.0 ± 8.7**	**9.9 ± 0.29**	**0.006**

WWE: women with epilepsy
N.S.: not statistically significant.
Statistical analysis was performed with independent sample t-test.

Prevalence of AED use during pregnancy

Data on AED use during pregnancy and the detected congenital malformations in each treatment group are presented in Table 13. Twenty patients (20.97%) were treatment-naive during pregnancy, while 71 women (79.03%) were exposed to various first- and second-generation AED regimens.

Of the total cohort, 30 women (32.95%) received monotherapy, while 41 (45.04%) were treated with combination therapy. Fourteen women (15.38%) received valproic acid (VPA) as monotherapy.

Seventeen women were treated with combination therapies that included VPA: 17.58% received a VPA + lamotrigine (LTG) combination, and 12.08% received

VPA + carbamazepine (CBZ). CBZ-containing monotherapy was administered in 10 cases (10.98%).

Combinations of LTG + CBZ and LTG + levetiracetam (LEV) were prescribed in 8 (8.79%) and 6 (6.59%) cases, respectively. LTG monotherapy was used in 6 women (6.59%).

Major congenital malformations (MCMs)

The rate of major congenital malformations (MCM) among neonates born to mothers exposed to AEDs was 7.69% (n = 7).

Four cases occurred following valproic acid (VPA) monotherapy: two cases of persistent ductus Botalli, one atrial septal defect, and one ventricular septal defect.

Two congenital malformations—gastroschisis and hypospadias—were observed after the administration of a valproic acid + carbamazepine combination.

One atrial septal defect was detected following carbamazepine monotherapy. (Table 13)

Table 13. Relationship between epilepsy syndromes, AED exposure during pregnancy and MCMs

PG: primary generalized epilepsy, PF: primary focal epilepsy, SG: secondary generalized epilepsy, SF: secondary focal epilepsy; WWE: women with epilepsy; AED: antiepileptic drug, MCM: major congenital malformation

Epilepsy syndrome	AED exposure during pregnancy	AED daily dosage (mg)	WWE (n=91)	WWE (%)	No. of MCMs
SF	**Not exposed to AED**	**-**	**20**	**20.97**	**0**
PG	**Valproic acid**	**500-1000**	**14**	**15.38**	**4**
SF	**Lamotrigine**	**50-500**	**6**	**6.59**	**0**
PG	**Carbamazepine**	**400-800**	**10**	**10.98**	**1**
PG	**Valproic acid + Lamotrigine**	**200-1800**	**16**	**17.58**	**1**
PG	**Valproic acid + Carbamazepine**	**100-1800**	**11**	**12.08**	**1**
PG	**Lamotrigine + Carbamazepine**	**100-1800**	**8**	**8.79**	**0**
SF SG	**Lamotrigine + Levetiracetam**	**100-1800**	**6**	**6.59**	**0**

Breastfeeding index in WWE versus non-WWE

The rate of breastfeeding was significantly lower among women with epilepsy (WWE) than among women without epilepsy. In the case group, 74.72% of all babies were breastfed, compared to 100% in the control group ($p = 0.019$).

III. Contraception

Maternal characteristics

The mean maternal age at delivery was similar in all the groups: 31-33 years old

Sociodemographic and Obstetric Characteristics

No significant differences were observed among the four groups regarding age, place of residence, number of children, or educational attainment. Similarly, perinatal outcomes were consistent across groups. However, perineal tears were reported more frequently among women who used effective contraceptive methods.

Breastfeeding Practices and Return of Menstruation

Exclusive breastfeeding at 6–8 weeks postpartum was more common among users of effective contraception or lactational amenorrhoea (LAM) compared to those relying on condoms or less effective methods. The return of menstruation by this time point was reported in 28.9% of effective method users, compared to 41.5% among condom users and 35.5% among users of less effective methods.

Sexual Activity and Contraceptive Knowledge

Table 14 summarises sexual activity patterns and specific knowledge related to postpartum contraception. Pre-pregnancy contraceptive use emerged as a strong predictor of postpartum contraceptive behaviour. The timing of resumption of sexual intercourse after childbirth was not significantly associated with the type of contraceptive method adopted. Women using less effective methods resumed sexual activity earlier (mean: 35.5 days postpartum), while users of effective methods resumed sexual activity slightly later (mean: 38.6 days).

Table 14. Contraceptive methods

Contraceptive Method	n	%
Effective Method Users	**135**	**22.5%**
- Progestogen-only pills (POPs)	**79**	**13.2%**
- Intrauterine device (IUD)	**18**	**3.0%**
- Postpartum female sterilisation	**16**	**2.7%**
- Levonorgestrel-releasing IUS (LNG-IUS)	**11**	**1.8%**
- Combined oral contraceptives (COCs)	**7**	**1.2%**
- Contraceptive vaginal ring	**4**	**0.7%**
LAM (intentional use)	**241**	**40.2%**
Condom Users	**130**	**21.7%**
Less Effective Method Users	**93**	**15.5%**
- Withdrawal	**36**	**6.0%**
- Spermicides	**3**	**0.5%**
- Periodic abstinence	**2**	**0.3%**
- Vaginal douching	**1**	**0.2%**
No Method Used	**51**	**8.5%**

The contraceptive method used during the first postpartum sexual encounter strongly predicted its continued use at 6–8 weeks: 74.8% of women who initially used an effective method continued with the same method. Use of effective contraception or LAM was also linked with higher frequency of sexual activity; 72.6% of effective method users and 62.2% of LAM users reported engaging in sexual intercourse at least once per week.

Approximately one-third of respondents understood that the introduction of formula or solid food increases the likelihood of fertility returning. Interestingly, women using LAM demonstrated a higher awareness that this method is not entirely reliable for pregnancy prevention ($p = .012$).

At 6–8 weeks postpartum, women's likelihood of adopting an effective contraceptive method was significantly associated with higher partner educational attainment (AOR 1.90; 95% CI: 1.27–2.84), resumption of menstruation (AOR 2.00; 95% CI: 1.25–3.23), and engaging in sexual intercourse at least once weekly (AOR 2.23; 95% CI: 1.44–3.48). Prior use of an

effective contraceptive method before pregnancy was a strong predictor, increasing the odds more than threefold (AOR 3.16; 95% CI: 2.10–4.76), while the application of such a method at first postpartum intercourse was also independently associated (AOR 1.03; 95% CI: 1.01–1.05) (Table 15).

Table 15. Prognostic factors of effective contraceptive use and intentional application of LAM in participants at 6–8 weeks postpartum

Prognostic factor	Use of an effective contraceptive method p Value	Use of an effective contraceptive method AOR (95% CI)	Use of LAM intentionally as a contraceptive method p Value	Use of LAM intentionally as a contraceptive method AOR (95% CI)
Partner's education	**.002**	**1.90 (1.27, 2.84)**	**.002**	**1.49 (1.07, 2.06)**
Return of menstruation	**.004**	**2.00 (1.25, 3.23)**	**–**	**–**
Frequency of sexual intercourse once a week	**<.001**	**2.23 (1.44, 3.48)**	**NA**	**NA**
Effective contraceptive method before pregnancy	**<.001**	**3.16 (2.10, 4.76)**	**<.001**	**0.39 (0.27, 0.57)**
Effective contraceptive method at first sexual intercourse after pregnancy	**.049**	**1.03 (1.01, 1.05)**	**–**	**–**
Aware of the fact that LAM is not fully effective in preventing pregnancy	**NA**	**NA**	**.012**	**1.57 (1.10, 2.22)**

a All variables were adjusted for age.

NA: not available.

Although an unfavourable financial situation and prior use of a less effective contraceptive method were more frequent among LAM users compared with non-users ($p < .05$; data not shown), these factors did not remain significant in multivariate analysis. LAM use at 6–8 weeks postpartum was positively associated with partner's higher educational level (AOR 1.49; 95% CI: 1.07–2.06) and inversely associated with previous use of a highly effective method before pregnancy (AOR 0.39; 95% CI: 0.27–0.57). Interestingly, awareness that LAM is not fully reliable as a contraceptive method was itself a significant positive predictor of its use (AOR 1.57; 95% CI: 1.10–2.22).

Used methods

Approximately 49% of participants resumed vaginal intercourse within 6–8 weeks postpartum, consistent with estimates reported elsewhere (41–61%) (136, 144–146). Most participants initiated contraception by 6–8 weeks (91.5%). Among them, 21.7% used condoms, and 15.5% used no method or a method of lower efficacy. LAM was intentionally used by 40.2%, whereas 22.5% used a highly effective method.

Contraceptive choice closely tracked infant-feeding practices: exclusive breastfeeding was associated with greater uptake of highly effective methods (47.4%). LAM users tended to have poorer financial backgrounds, in contrast to reports from other countries (146–149). International patterns of exclusive breastfeeding vary (USA 44.4%, Canada 51.7%, Australia 39% at 3 months; UK 55% at 6 weeks), which aligns with our cohort (57.1% at 6–8 weeks) (147–150).

DISCUSSION

Pregnancy in women with multiple sclerosis (MS) and epilepsy is relatively rare and requires a specialized approach and close monitoring by both neurologists and obstetrician-gynecologists. Collaboration between these specialists is essential, and they must rely on evidence-based information to counsel patients and their families.

The prevalence of fertility problems requiring assisted reproductive technology (ART) in our MS population was low (3.07%), suggesting that MS does not negatively affect fertility—at

least in its early stages. In our study, all ART-treated women belonged to the relapsing-remitting MS subgroup.

Finkelsztejn et al. (158) reported a high rate of early pregnancy loss in women with MS, with a mean miscarriage rate of 23.8% (range: 24.9–31.8%). In 1998, Nelson et al. hypothesized that these adverse outcomes might be related to circulating maternal antibodies during pregnancy (159–170). However, that study was limited by the absence of a healthy control group.

To minimize bias in our analysis, we included a matched neurologically healthy control group when evaluating pregnancy outcomes in women with MS. The significantly higher rate of hospitalization (>5 days) in the MS group compared to controls may be partially explained by comorbid depressive disorders (158).

In our cohort, the rate of miscarriage in the first trimester was significantly higher (18.46%) among women with MS, as was the rate of intrauterine death in the third trimester (7.69%) compared to women without MS ($p < 0.001$ and $p = 0.035$, respectively).

It is widely accepted that multigravida women have a higher risk of foetal loss. Similarly, in our study, the rates of miscarriage and intrauterine death were significantly higher in the multigravida group compared to the primigravida group ($p = 0.003$ and $p = 0.008$, respectively). These findings suggest that women with multiple sclerosis have an increased risk of miscarriage and intrauterine death compared to the general population—particularly among multigravidas.

A literature review by Finkelsztejn et al. (158) reported a mean caesarean section rate of 41.5% (range: 40.5–42.4%) among women with MS in various countries. Dahl et al. (173, 174) similarly observed a significantly higher caesarean section rate among women with MS than among healthy controls.

In our study, the caesarean section rate was significantly higher among both primigravida and multigravida women with MS compared to controls ($p = 0.002$). Vaginal delivery was significantly less common in multigravida women (with or without MS) than in primigravidas ($p = 0.009$). The higher rate of caesarean section in women with MS may be partially attributed to the caution exercised by obstetricians and gynaecologists due to unfavourable medical histories ($p = 0.002$).

We also observed a higher rate of twin pregnancies in the MS group compared to controls ($p = 0.095$). To our knowledge, this finding has not been reported by other authors.

Additionally, we found that the degree of disability—as measured by the Expanded Disability Status Scale (EDSS)—was low in both subgroups (1.36 ± 1.2 in primigravidas and 1.48 ± 4.4 in multigravidas), and the mean duration of MS was 3.28 years. These findings suggest that elective termination of pregnancy based solely on MS diagnosis may not be justified.

The average birth weight and the rates of small for gestational age, preterm birth, post-term birth, and postpartum complications in the MS group did not differ significantly from those in the healthy control group. Our findings are consistent with those of Ramagopalan et al. (171, 172), who concluded that MS does not negatively affect neonatal outcomes. However, other authors have reported higher rates of low birth weight and prematurity than observed in our study (173–176).

A meta-analysis by Finkelsztejn et al. (158) indicated an increased prevalence of congenital malformations and neonatal death (range: 0.37%–3.30%). In our MS subgroup, no congenital malformations were detected. However, the rate of intrauterine death in our MS population (11.6%) was higher than that reported in the Finkelsztejn meta-analysis. The cause of intrauterine death remains unclear in our cases.

Obesity was more frequent in the general population than among women with epilepsy (WWE) ($p < 0.001$). Our findings align with those of Bunyan et al. (123), who found a significantly higher rate of hypertensive disorders among WWE compared to controls.

In the study by Thomas et al. (129), WWE experienced three peaks of seizure relapse during pregnancy—specifically in the first, second, and sixth months—with the highest seizure frequency occurring in the first three days postpartum. Our data are consistent with these findings in a larger population.

In agreement with earlier reports (125–128), we observed a significantly higher miscarriage rate among WWE compared to controls ($p = 0.001$), suggesting that epilepsy may contribute to pregnancy loss.

Recent studies (129, 131) have also shown a higher caesarean section rate in WWE compared to non-epileptic women. In contrast, Katz et al. (125) concluded that maternal epilepsy is not a predisposing factor for caesarean delivery. Similarly, other authors (177–185) have found no significant differences in caesarean section rates among WWE.

In our cohort, however, the caesarean section rate was significantly higher in the epilepsy group compared to the control group ($p = 0.022$). Epilepsy thus appears to be a frequent co-indication for caesarean section in our population.

We also found that the incidence of post-term birth was significantly higher among WWE than among non-WWE ($p < 0.001$). This is in line with findings by Yerby et al. (178), who reported that epilepsy is associated with a 2.79-fold increased risk of preeclampsia.

Discontinuation of pharmacological therapy is not feasible in most cases, as seizures during pregnancy can be life-threatening and may expose both the mother and fetus to greater risks than those posed by the treatment itself (88–91).

Previous studies have reported strong correlations between maternal exposure to antiepileptic drugs (AEDs) and significantly lower birth weight, intrauterine growth restriction, and smaller head circumference in newborns (182–185). In contrast to these findings, our study revealed significantly lower average birth weight, mean birth length, head circumference, and chest circumference in newborns of WWE compared to non-WWE ($p = 0.003$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Additionally, 1-, 5-, and 10-minute Apgar scores, as well as umbilical cord blood pH, were significantly lower in the WWE group ($p < 0.001$, $p < 0.001$, $p < 0.006$, and $p < 0.001$, respectively).

The mean gestational age at delivery and the rate of preterm birth did not differ significantly between the two groups. Our findings contrast with those of Cassina et al. (48), who reported a significantly higher preterm birth rate and lower mean gestational age in WWE compared to controls.

Holmes et al. (102) demonstrated that the phenotype of major congenital malformations is strongly associated with specific AEDs, with congenital heart defects most commonly observed among WWE exposed to carbamazepine. In agreement with their findings, we observed one case of atrial septal defect in a newborn whose mother received carbamazepine monotherapy.

Valproic acid use during pregnancy—especially at doses above 1000 mg/day—is known to be associated with an increased risk of spina bifida compared to other AEDs (88–91). In our cohort, a higher rate of major congenital malformations (MCMs) was observed among women receiving single-agent AED therapy. However, multiple studies have shown that the teratogenic risk is considerably higher in AED polytherapy than in monotherapy (100–111).

Numerous studies have also demonstrated that dietary folic acid supplementation during the periconceptional period reduces the risk of congenital malformations—particularly anencephaly and spina bifida. It has also been suggested that high folic acid levels may reduce the risk of heart defects, cleft palate, and limb abnormalities.

Breastfeeding is widely recognized for its beneficial effects; however, concerns remain regarding the potential impact of AED exposure through breast milk on the cognitive development of the newborn (100–113).

A review by Crawford indicated that women with epilepsy (WWE) should be encouraged to breastfeed their infants. The concentration profile of various AEDs in breast milk generally mirrors that in maternal plasma. Importantly, the total amount of AEDs transferred via breast milk is usually much lower than the amount transferred across the placenta during pregnancy. However, because drug elimination mechanisms are immature in early infancy, repeated exposure through breastfeeding may lead to accumulation in the newborn (112).

A large prospective multicenter observational study (114) reported that adverse cognitive effects following in utero exposure to valproic acid may persist for up to six years. In light of these concerns, the breastfeeding rate among WWE in our cohort was relatively low.

Contraception: At 6–8 weeks postpartum, 49% of participants had resumed vaginal intercourse, and 91.5% reported using some form of contraception. Highly effective methods were used by 22.5% of women, condoms by 21.7%, and less effective or no methods by 15.5%. LAM was intentionally used by 40.2% of participants.

Contraceptive choice was closely linked to feeding practices: exclusive breastfeeding was associated with greater use of effective methods, while LAM users tended to have poorer financial backgrounds. Financial status, however, was not an independent predictor of method effectiveness. Regular sexual activity, as well as previous use of effective methods before pregnancy or at first postpartum intercourse, strongly predicted current effective method use. Infrequent sexual activity and prior use of less effective methods were associated with LAM or other low-efficacy options.

Use of long-acting reversible contraception (LARC) was rare (4.8% for intrauterine devices, none for implants). Partner's higher education, rather than the woman's own, emerged as a significant predictor of effective contraceptive use. The return of menstruation and history of effective method use also increased the likelihood of continued effective contraception. Interestingly, LAM was more common among those aware of its limitations, possibly due to convenience or economic reasons.

Financial dependence did not differentiate between less and more effective method use in this sample, diverging from our earlier observation that lower income discourages the adoption of modern methods (151). Other evidence nonetheless implicates financial dependence in postpartum contraceptive choice (136, 152).

Consistent with prior work (139, 145, 151, 153), frequent sexual intercourse was a key determinant of continued hormonal or other effective method use, whereas infrequent coitus was linked to reliance on less effective approaches (e.g., condoms, vaginal douching, spermicides, withdrawal). Prior reliance on less effective methods—before pregnancy and at first postpartum intercourse—strongly predicted continued use of such methods or adoption of LAM (154). Loewenberg Weisband et al. likewise showed that previous contraceptive practice shapes current method selection (154). Postpartum condom use was most common among women who had resumed menstruation, reported frequent intercourse, and had used a less effective method before pregnancy (≈30%).

Although LARC (IUD, LNG-IUS, subdermal implant) is safe and highly effective for lactating women and can be initiated immediately or soon after delivery (155, 156), uptake was very low: 4.8% used intrauterine contraception and none used a subdermal implant. Potential contributors—unassessed here—include financial barriers, limited knowledge, inadequate counselling, or plans for further pregnancies (156).

Obstetric and sociodemographic characteristics did not predict method choice at 6–8 weeks postpartum. Higher partner educational attainment was associated with greater odds of effective method use, whereas prior literature has more often highlighted the woman's education (145, 151, 156).

In adjusted analyses, previous use of an effective method and the return of menstruation were central predictors of continued use of that method postpartum, consistent with earlier reports (144, 156). Intentional LAM use persisted despite recognition of its limitations, likely reflecting convenience and cost considerations. According to recent data, mostly the young parents are not educated well about contraception. They need more convenient tools to reach, like community media or standalone AI solutions, that can answer the most intime questions correctly and securely (157).

NEW OBSERVATIONS AND RECOMMENDATIONS OF THE THESIS

Based on the comprehensive evaluation presented in this thesis, several novel observations and practical recommendations can be proposed:

1. Multiple Sclerosis (MS) and Pregnancy Outcomes

- Our study revealed significantly higher rates of miscarriage and intrauterine death among women with MS—particularly in multigravidas—suggesting a potential cumulative adverse effect over successive pregnancies. Enhanced antenatal monitoring is especially recommended for multigravida MS patients.

- The high prevalence of depressive disorders among pregnant women with MS underscores the need to incorporate routine psychological support and mental health screening into standard antenatal care protocols for this population.

2. Epilepsy Management During Pregnancy

- The findings highlight a high prevalence of pre-existing hypertension and preeclampsia among women with epilepsy (WWE), supporting the need for comprehensive cardiovascular risk assessment and management as part of routine prenatal care.
- The elevated incidence of seizures in the third trimester emphasizes the importance of therapeutic drug monitoring and timely dosage adjustments of antiepileptic drugs, particularly in late pregnancy.
- Given the teratogenic risks associated with valproic acid (VPA), its use should be minimized in women who are pregnant or planning pregnancy, with a preference for safer alternative medications when feasible.

3. Contraception Practice

- Use of long-acting reversible contraception (LARC) was rare (4.8% for intrauterine devices, none for implants). Partner's higher education, rather than the woman's own, emerged as a significant predictor of effective contraceptive use.
- The return of menstruation and history of effective method use also increased the likelihood of continued effective contraception.
- Interestingly, LAM was more common among those aware of its limitations, possibly due to convenience or economic reasons.
- Medical professionals must find effective ways to educate younger generations, including community media and standalone AI solutions.

4. General Recommendations for Clinical Practice

- A multidisciplinary approach involving obstetricians, neurologists, psychiatrists, pediatricians, and geneticists is crucial to optimize maternal and neonatal outcomes in pregnancies affected by neuropsychiatric conditions.
- The development of standardized clinical guidelines and comprehensive patient education on risk factors, disease management, and medication safety during pregnancy is strongly recommended.

- Further prospective, longitudinal research is essential to clarify the complex relationships among neuropsychiatric disorders, pregnancy, medication exposure, and long-term developmental outcomes in offspring.
- To reduce unintended pregnancies, the availability and uptake of reliable postpartum contraception should be prioritised. Strategies to promote immediate or early LARC initiation, enhance public awareness of highly effective methods, and ensure targeted training for health care providers are warranted.

LIMITATIONS OF THE THESIS

Due to insufficient data, we were unable to report on maternal smoking, psychoactive drug use, folic acid intake, use of antidepressants during the prenatal period, and breastfeeding rates among women.

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REFERENCES

1. Compston A & Coles A (2002). Multiple sclerosis. Lancet 359: 1221-1231.
2. Salama, M., El-Samahy, M., Anani, M. M., Attia, F., Amer, S. A., Ahmed, S. H., ... & Saleh, R. M. (2025). Assessment of Herpes virus infection and Cytomegalovirus infection and their relation to multiple sclerosis. *The Egyptian journal of immunology*, *32*(2), 27-34.
3. Bencsik K, Rajda C, Klivényi P, Járdánházy T, Vécsei L. The prevalence of multiple sclerosis in the Hungarian city of Szeged. Acta Neurol Scand. 1998 May;97(5):315-9.
4. Mátyás, K., Bobál, T., & Abonyi, Z. (2023). Compliance-és betegútvizsgálat betegségmódosító kezelés alatt álló sclerosis multiplexes betegeknél. *IDEGGYÓGYÁSZATI SZEMLE/CLINICAL NEUROSCIENCE*, *76*(9-10), 309-317.
5. Confavreux C & Vukusic S (2006). Natural history of multiple sclerosis: a unifying concept. Brain 129: 606-616.
6. Oost, W., Meilof, J. F., & Baron, W. (2025). Multiple sclerosis: what have we learned and can we still learn from electron microscopy. *Cellular and Molecular Life Sciences*, *82*(1), 1-22.
7. Weinshenker BG, Hader W, Carriere W, Baskerville J, Ebers GC (1989). The influence of pregnancy on disability from multiple sclerosis: a population-based study in Middlesex County, Ontario. Neurology 39: 1438-1440.
8. Houtchens, M. K., Manieri, M. C., Mahlanza, T. D., Pol-Patil, J., Klawiter, E. C., Solomon, A. J., ... & Sadovnick, A. D. (2025). A Real-World Prospective Multiple Sclerosis Pregnancy Registry in the United States: PREG-MS. *Neurology: Clinical Practice*, *15*(2), e200425.
9. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L (1998). Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998. 338: 278-285.
10. Arredondo-Robles, A. V., Rodríguez-López, K. P., & Ávila-Avilés, R. D. (2025). Clinical Management in Multiple Sclerosis. *Neuroglia*, *6*(1), 6.
11. McFarland HF, Martin R (2007). Multiple sclerosis: a complicated picture of autoimmunity. Nat Immunol 8: 913-919
12. Nasrabadi, M. E., Al-Harrasi, A., Mohammadi, S., Zarif Azam Kardani, F., Rahmati, M., & Memarian, A. (2025). Pioglitazone as a potential modulator in autoimmune diseases: a review on its effects in systemic lupus erythematosus, psoriasis,

inflammatory bowel disease, and multiple sclerosis. *Expert Review of Clinical Immunology*, *21*(1), 5-15.

13. Miller DH (2004). Biomarkers and surrogate outcomes in neurodegenerative disease: lessons from multiple sclerosis. NeuroRx 1: 284-294.
14. Young, C. A., Rog, D. J., Sharrack, B., Tanasescu, R., Kalra, S., Harrower, T., ... & Mills, R. J. (2024). Correlates and trajectories of relapses in relapsing–remitting multiple sclerosis. *Neurological Sciences*, *45*(5), 2181-2189.
15. Confavreux C, Vukusic S, Adeleine P (2003). Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126: 770-782.
16. Portaccio, E., Magyari, M., Havrdova, E. K., Ruet, A., Brochet, B., Scalfari, A., ... & Amato, M. P. (2024). Multiple sclerosis: emerging epidemiological trends and redefining the clinical course. *The Lancet Regional Health–Europe*, *44*.
17. Myhr KM, Grytten N, Aarseth JH, & Nyland H (2006). The Norwegian Multiple Sclerosis National Competence Centre and National Multiple Sclerosis registry - a resource for clinical practice and research. Acta Neurol Scand 113 (suppl. 183): 37-40.
18. Tigchelaar, C., Atmosoerodjo, S. D., van Faassen, M., Wardenaar, K. J., De Deyn, P. P., Schoevers, R. A., ... & Absalom, A. R. (2021). The Anaesthetic Biobank of Cerebrospinal fluid: a unique repository for neuroscientific biomarker research. *Annals of Translational Medicine*, *9*(6), 455.
19. Bronnum-Hansen H, Koch-Henriksen N, & Stenager E (2004). Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 127: 844-850.
20. Qian, Z., Li, Y., Guan, Z., Guo, P., Zheng, K., Du, Y., ... & Zhang, M. (2023). Global, regional, and national burden of multiple sclerosis from 1990 to 2019: findings of global burden of disease study 2019. Frontiers in public health, 11, 1073278.
21. Kantarci O & Wingerchuk D (2006). Epidemiology and natural history of multiple sclerosis: new insights. Curr Opin Neurol 19: 248-254.
22. Santoleri, F., Lasala, R., Berardini, E., Vernacchio, F., Leo, D., & Costantini, A. (2024). Adherence, Persistence, Switching and Costs of Injectable and Oral Therapies for Multiple Sclerosis. Real Life Analysis Over 6 Years of Treatment. *Hospital Pharmacy*, *59*(4), 476-484.
23. Ebers GC (2005). A twin consensus in MS. Mult Scler 11: 497-499.
24. Cozart, J. S. (2021). *Modifying Diet and Exercise in Multiple Sclerosis: A Pilot Study*. University of Missouri-Kansas City.

25. Sawcer S, Ban M, Maranian M, Yeo TW, Compston A, Kirby A, Daly MJ, De Jager PL, Walsh E, Lander ES, Rioux JD, Hafler DA, Ivinson A, Rimmler J, Gregory SG, Schmidt S, Pericak-Vance MA, Akesson E, Hillert J, Datta P, Oturai A, Ryder LP, Harbo HF, Spurkland A, Myhr KM, Laaksonen M, Booth D, Heard R, Stewart G, Lincoln R, Barcellos LF, Hauser SL, Oksenberg JR, Kenealy SJ, & Haines JL (2005). A high-density screen for linkage in multiple sclerosis. *Am J Hum Genet* 77: 454-467.
26. Mazdeh, M., Noroozi, R., Komaki, A., Azari, I., Ghafouri-Fard, S., & Taheri, M. (2019). A single nucleotide polymorphism in the metabotropic glutamate receptor 7 gene is associated with multiple sclerosis in Iranian population. *Multiple sclerosis and related disorders*, *28*, 189-192.
27. Baecher-Allan, C., Kaskow, B. J., & Weiner, H. L. (2018). Multiple sclerosis: mechanisms and immunotherapy. *Neuron*, *97*(4), 742-768.
28. Cabre P (2007). Migration and multiple sclerosis: the French West Indies experience. J Neurol Sci 262: 117-121.
29. Mpakosi, A., Cholevas, V., Tzouvelekis, I., Passos, I., Kaliouli-Antonopoulou, C., & Mironidou-Tzouveleki, M. (2024, September). Autoimmune diseases following environmental disasters: a narrative review of the literature. In *Healthcare* (Vol. 12, No. 17, p. 1767). MDPI.
30. Dean G, Elian M (1997). Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis. J Neurol Neurosurg Psychiatry 63: 565-568.
31. Alonso-Magdalena, L., i Codina, O. C., Zia, E., Sundström, P., & Pessah-Rasmussen, H. (2024). Prevalence and disease disability in immigrants with multiple sclerosis in Malmö, southern Sweden. *Clinical neurology and neurosurgery*, *240*, 108255.
32. Ascherio A, Munger KL (2007). Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol 61: 288-299.
33. Frisch, E. S. (2024). The effect of Natalizumab on functional properties of monocytes in patients with Multiple Sclerosis.
34. Serafini B, Rosicarelli B, Franciotta D, Magliozzi R, Reynolds R, Cinque P, Andreoni L, Trivedi P, Salvetti M, Faggioni A, & Aloisi F (2007). Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. J Exp Med 204: 2899-2912.
35. Martinelli, S., Nannini, G., Cianchi, F., Coratti, F., & Amedei, A. (2024). The impact of microbiota–immunity–hormone interactions on autoimmune diseases and infection. *Biomedicines*, *12*(3), 616.

36. Ascherio A & Munger KL (2007). Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 61: 504-513.
37. Barbero Mazzucca, C., Scotti, L., Comi, C., Vecchio, D., Chiocchetti, A., & Cappellano, G. (2024). The role of diet in multiple sclerosis onset: A prospective study using UK Biobank. *Nutrients*, *16*(11), 1746.
38. Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, & Ascherio A (2004). Vitamin D intake and incidence of multiple sclerosis. Neurology 62: 60-65.
39. Yu, X. H., Lu, H. M., Li, J., Su, M. Z., Li, X. M., & Jin, Y. (2024). Association between 25 (OH) vitamin D and multiple sclerosis: cohort, shared genetics, and Causality. *Nutrition Journal*, *23*(1), 151.
40. Munger KL, Levin LI, Hollis BW, Howard NS, & Ascherio A (2006). Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 296: 2832-2838.
41. Balasooriya, N. N., Elliott, T. M., Neale, R. E., Vasquez, P., Comans, T., & Gordon, L. G. (2024). The association between vitamin D deficiency and multiple sclerosis: An updated systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders*, 105804.
42. Hayes CE, Nashold FE, Spach KM, & Pedersen LB (2003). The immunological functions of the vitamin D endocrine system. Cell Mol Biol 49: 277-300.
43. Pana, A., Muntean, I. E., & Pitea, A. M. (2024). The impact of vitamin D in type 1 diabetes in pediatric patients. *Romanian medical JouRnal*, *71*(3).
44. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, & Tourtellotte WW (1983). New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13: 227-31.
45. Habbestad, A., Willumsen, J. S., Aarseth, J. H., Grytten, N., Midgard, R., Wergeland, S., ... & Torkildsen, Ø. (2024). Increasing age of multiple sclerosis onset from 1920 to 2022: a population-based study. *Journal of Neurology*, *271*(4), 1610-1617.
46. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den NS, Weinshenker BY, Wolinsky JS (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel in the diagnosis of multiple sclerosis. Ann Neurol 50: 121-127.

47. Zahoor, I., Waters, J., Ata, N., Datta, I., Pedersen, T. L., Cerghet, M., ... & Giri, S. (2024). Blood-based targeted metabolipidomics reveals altered omega fatty acid-derived lipid mediators in relapsing-remitting multiple sclerosis patients. *bioRxiv*.

48. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292-302.
49. Jendretzky, K. F., Lezius, L. M., Thiele, T., Konen, F. F., Huss, A., Heitmann, L., ... & Skripuletz, T. (2024). Prevalence of comorbid autoimmune diseases and antibodies in newly diagnosed multiple sclerosis patients. *Neurological Research and Practice*, *6*(1), 55.
50. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Radu EW, Bauer L, Dahms S, Lanius V, Pohl C, & Sandbrink R (2007). Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 370: 389-397.
51. Mansurov, A., Lauterbach, A., Budina, E., Alpar, A. T., Hubbell, J. A., & Ishihara, J. (2021). Immunoengineering approaches for cytokine therapy. *American Journal of Physiology-Cell Physiology*, *321*(2), C369-C383.
52. Garcia MA & Blasco MR (2007). Confirming the MS diagnosis. Int MS J 14: 58-63.
53. Fernandez, O., Sörensen, P. S., Comi, G., Vermersch, P., Hartung, H. P., Leocani, L., ... & Oreja-Guevara, C. (2024). Managing multiple sclerosis in individuals aged 55 and above: a comprehensive review. *Frontiers in Immunology*, *15*, 1379538.
54. Ostensen M & Villiger PM (2007). The remission of rheumatoid arthritis during pregnancy. Semin Immunopathol 29: 185-191.
55. Hoseini, S., Hosseini, E. S., Abessi, P., & Montazeri, F. (2024). Paracrine secretions and immunological activities of human mesenchymal stem cells; the key regenerative factors of microenvironment. *Journal of Stem Cell Research & Therapy*, *14*(1), 636.
56. Voskuhl RR (2003). Hormone-based therapies in MS. Int MS J 10: 60-66.
57. Sicotte NL, Liva SM, Klutch R, Pfeiffer P, Bouvier S, Odesa S, Wu TC, & Voskuhl RR (2002). Treatment of multiple sclerosis with the pregnancy hormone estriol. Ann Neurol 52: 421-428.

58. Martinelli, S., Nannini, G., Cianchi, F., Coratti, F., & Amedei, A. (2024). The impact of microbiota–immunity–hormone interactions on autoimmune diseases and infection. *Biomedicines*, *12*(3), 616.
59. Houtchens MK (2007). Pregnancy and multiple sclerosis. Semin Neurol 27: 434-441.
60. Jaakkola N, Jaakkola MS, Gissler M, & Jaakkola JJ (2001). Smoking during pregnancy in Finland: determinants and trends, 1987-1997. Am J Public Health 91: 284-286.
61. Ekblad, M. O., Gissler, M., & Korhonen, P. E. (2025). Association between maternal smoking, isolated proteinuria during pregnancy and preterm birth: a Finnish registry analysis. *Kidney International Reports*, *10*(1), 169-176.
62. Saito S (2000). Cytokine network at the feto-maternal interface. J Reprod Immunol 47: 87-103.
63. Dutta, S., Sengupta, P., & Liew, F. F. (2024). Cytokine landscapes of pregnancy: mapping gestational immune phases. *Gynecology and Obstetrics Clinical Medicine*, *4*(1).
64. Al-Shammri S, Rawoot P, Azizieh F, AbuQoora A, Hanna M, Saminathan TR, & Raghupathy R (2004). Th1/Th2 cytokine patterns and clinical profiles during and after pregnancy in women with multiple sclerosis. J Neurol Sci 222: 21-27. Altman DG (1991). Practical statistics for medical research. London: Chapman & Hall/CRC.
65. Kancheva, R., Hill, M., Velíková, M., Kancheva, L., Včelák, J., Ampapa, R., ... & Kubala Havrdová, E. (2024). Altered Steroidome in Women with Multiple Sclerosis. *International Journal of Molecular Sciences*, *25*(22), 12033.
66. van den Broek HH, Damoiseaux JG, De Baets MH, & Hupperts RM (2005). The influence of sex hormones on cytokines in multiple sclerosis and experimental autoimmune encephalomyelitis: a review. Mult Scler 11: 349-359.
67. Faraji, J., Bettenson, D., Babatunde, S., Gangur-Powell, T., Yong, V. W., & Metz, G. A. (2022). Thermoregulatory dynamics reveal sex-specific inflammatory responses to experimental autoimmune encephalomyelitis in mice: Implications for multiple sclerosis-induced fatigue in females. *Brain, Behavior, & Immunity-Health*, *23*, 100477.
68. Zenclussen AC, Schumacher A, Zenclussen ML, Wafula P, & Volk HD (2007). Immunology of pregnancy: cellular mechanisms allowing foetal survival within the maternal uterus. Expert Rev Mol Med 9: 1-14.
69. Weng, J., Couture, C., & Girard, S. (2023). Innate and adaptive immune systems in physiological and pathological pregnancy. *Biology*, *12*(3), 402.

70. Takahashi T & Sakaguchi S (2003). The role of regulatory T cells in controlling immunologic self-tolerance. Int Rev Cytol 225: 1-32.
71. Ruiz Pérez, M., Vandenabeele, P., & Tougaard, P. (2024). The thymus road to a T cell: migration, selection, and atrophy. *Frontiers in Immunology*, *15*, 1443910.
72. Airas L, Saraste M, Rinta S, Elovaara I, Huang YH, & Wiendl H (2007). Immunoregulatory factors in multiple sclerosis patients during and after pregnancy: relevance of natural killer cells. Clin Exp Immunol 151: 235-243.
73. Ronchetti, C., Cirillo, F., Di Segni, N., Cristodoro, M., Busnelli, A., & Levi-Setti, P. E. (2022). Inflammatory bowel disease and reproductive health: from fertility to pregnancy—a narrative review. *Nutrients*, *14*(8), 1591.
74. Bielekova B, Catalfamo M, Reichert-Scrivner S, Packer A, Cerna M, Waldmann TA, McFarland H, Henkart PA, & Martin R (2006). Regulatory CD56 (bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis. Proc Natl Acad Sci USA 103: 5941-5946.
75. Ronchetti, C., Cirillo, F., Di Segni, N., Cristodoro, M., Busnelli, A., & Levi-Setti, P. E. (2022). Inflammatory bowel disease and reproductive health: from fertility to pregnancy—a narrative review. *Nutrients*, *14*(8), 1591.
76. Dahl J, Myhr KM, Daltveit AK, Hoff JM, Gilhus NE: Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology. 2005;65:1961-3.
77. Rahmati, S., Galavi, Z., Kavyani, B., Arshadi, H., Geerts, J., & Sharifi, H. (2024). Maternal and neonatal outcomes in pregnant women with multiple sclerosis disease: A systematic review and meta-analysis. *Midwifery*, 104004.
78. Lu E, Dahlgren L, Sadovnick A, Sayao A, Synnes A, Tremlett H. Perinatal outcomes in women with multiple sclerosis exposed to disease-modifying drugs. Mult Scler. 2012 Apr;18(4):460-7.
79. Alhomoud, M. A., Khan, A. S., & Alhomoud, I. (2021). The potential preventive effect of pregnancy and breastfeeding on multiple sclerosis. *European Neurology*, *84*(2), 71-84.
80. Salminen HJ, Leggett H, Boggild M. Glatiramer acetate exposure in pregnancy: preliminary safety and birth outcomes. J Neurol. 2010 Dec;257(12):2020-3.
81. Kaplan, S., Ghimpeteanu, A., & Dragut, C. F. (2025). Pregnancy and Infant Outcomes in Women with Multiple Sclerosis Exposed to Glatiramer Acetate Therapy: An Extended 4-Year Safety Update. *Drug Safety*, 1-17.

82. Fragoso YD. Glatiramer acetate to treat multiple sclerosis during pregnancy and lactation: a safety evaluation. Expert Opin Drug Saf. 2014 Dec;13(12):1743-8.
83. Graber, M., Panchaud, A., Legardeur, H., Derfuss, T., Friedli, C., Gobbi, C., ... & Chan, A. (2024). Recommendations for the Treatment of Multiple Sclerosis in Family Planning, Pregnancy and Lactation in Switzerland: Immunotherapy. *Clinical and Translational Neuroscience*, *8*(3), 26.
84. Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe – a systematic review. Eur J Neurol. 2005;12(4):245-53.
85. Antaya, T. C., Espino-Alvarado, P. H., Oiamo, T., Wilk, P., Speechley, K. N., & Burneo, J. G. (2024). Association of outdoor air and noise pollution with unprovoked seizures and new onset epilepsy: A systematic review and meta-analysis. *Epilepsia*, *65*(7), 1847-1867.
86. Saleh AM, Abotalib ZM, Al-Ibrahim AA, Al-Sultan SM. Comparison of maternal and foetal outcomes in epileptic and non-epileptic women. Saudi Med J. 2008;29:261-66.
87. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. Epilepsia 2003;44:11-20.
88. 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.
89. Wan, X., Wu, Y., Zou, Q., Yuan, B., Huang, L., & Hu, M. (2024). Seizure control and adverse outcomes of lamotrigine use during pregnancy: A systematic review and meta-analysis. *Epilepsy & Behavior*, *157*, 109924.
90. Cassina M, Dilaghi A, Di Gianantonio E, Cesari E, De Santis M, Mannaioni G, Pistelli A, Clementi M.Pregnancy outcome in women exposed to antiepileptic drugs: Teratogenic role of maternal epilepsy and its pharmacologic treatment. Reprod Toxicol. 2013 13;39C:50-57
91. Mawhinney E, Campbell J, Craig J, Russell A, Smithson W, Parsons L, Robertson I, Irwin B, Morrison P, Liggan B, Delanty N, Hunt S, Morrow J.Valproate and the risk for congenital malformations: Is formulation and dosage regime important? Seizure. 2012;21:215-8.

92. Csáky-Szunyogh M, Vereczkey A, Kósa Z, Urbán R, Czeizel AE. Association of maternal diseases during pregnancy with the risk of single ventricular septal defects in the offspring - a population-based case-control study. J Matern Foetal Neonatal Med. 2013 26(8):738-47.
93. Zegelbone, P. M., & Patel, S. S. (2024). Teratogenic Factors Contributing to the Development of Congenital Heart Defects. In *Pediatric Cardiology: Foetal, Pediatric, and Adult Congenital Heart Diseases* (pp. 149-174). Cham: Springer International Publishing.
94. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Effects of foetal antiepileptic drug exposure: outcomes at age 4.5 years. Neurology. 2012;78:1207-14.
95. Angus-Leppan, H., Arkell, R., Watkins, L., Heaney, D., Cooper, P., & Shankar, R. (2024). New valproate regulations, informed choice and seizure risk. *Journal of Neurology, 271*(8), 5671-5686.
96. Laine-Cessac P, Le Jaoen S, Rosenau L, Gamelin L, Allain P, Grosieux P. Uncontrolled retrospective study of 75 pregnancies in women treated for epilepsy. J Gynecol Obstet Biol Reprod (Paris) 1995;24:537-42.
97. Crawford P. Epilepsy and pregnancy: good management reduces the risks. Prof Care Mother Child 1997;7:17-8.
98. Hong, J., Crawford, K., Cavanagh, E., da Silva Costa, F., & Kumar, S. (2024). Prediction of preterm birth in growth-restricted and appropriate-for-gestational-age infants using maternal PlGF and the sFlt-1/PlGF ratio—A prospective study. *BJOG: An International Journal of Obstetrics & Gynaecology, 131*(8), 1089-1101.
99. Denise S Hill, Bogdan J Wlodarczyk, Ana M Palacios, Richard H Finnell Teratogenic effects of antiepileptic drugs Expert Rev Neurother. 2010 June; 10(6): 943–959.
100. Perucca E. Birth defects after prenatal exposure to antiepileptic drugs. Lancet Neurol 2005;4:781-6. Page 17 of 28Group. Effects of breastfeeding in children of women taking antiepileptic drugs Neurology. 2010;75:1954-60.
101. Bromfield EB, Dworetzky BA, Wyszynski DF, Smith CR, Baldwin EJ, Holmes LB. Valproate teratogenicity and epilepsy syndrome. Epilepsia 2008;49:2122-4.
102. Ornoy, A., Echefu, B., & Becker, M. (2023). Valproic acid in pregnancy revisited: neurobehavioral, biochemical and molecular changes affecting the embryo and fetus in

humans and in animals: a narrative review. International Journal of Molecular Sciences,25(1), 390.

103. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia 2009;50:2130-9.

104. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol 2012;11:803-13.

105. Ji, Z., Nie, J., Shen, Q., & Fu, Z. (2025). Antiepileptic drugs and foetal disorders: analysis of 20-year data from the pharmacovigilance center. Frontiers in Pharmacology, 16, 1556598.

106. Morrow JI, Hunt SJ, Russell AJ, Smithson WH, Parsons L, Robertson I, Waddell R, Irwin B, Morrison PJ, Craig JJ. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psych 2009;80:506-11.

107. Conei, D., Rojas, M., Santamaría, L., & Risopatrón, J. (2024). Teratogenicity of Valproic Acid: Can Reverse its Possible Effects on Testicular Development with Vitamin E?. International Journal of Morphology, 42(4).

108. Pennell PB. Pregnancy in the woman with epilepsy: maternal and foetal outcomes. Semin Neurol 2002;22:299-308.

109. Costa, B., & Vale, N. (2024). Advances in psychotropic treatment for pregnant women: efficacy, adverse outcomes, and therapeutic monitoring. Journal of Clinical Medicine, 13(15), 4398.

110. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010;362:2185-93.

111. Qu, P., Zhang, S., Chen, J., Li, X., Zhao, D., Liu, D., ... & Dang, S. (2024). Risk-prediction nomogram for congenital heart disease in offspring of Chinese pregnant women. BMC Pregnancy and Childbirth, 24(1), 509.

112. Crawford P. Best Practice Guidelines for the Management of Women with Epilepsy. Epilepsia 2005;46:117-24.

113. Siqin, L., Jia, S. O. N. G., Shiming, H., Xiaoli, Y. U. A. N., Yan, P., Congcai, G. U., & Zucai, X. (2024). Prepregnancy fertility guidance for women of childbearing age with epilepsy: A scoping review. International Journal of Nursing Studies Advances, 100276.

114. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M et al. Cognitive function at 3 years of age after foetal exposure to antiepileptic drugs. N Engl J Med 2009;360:1597-605.
115. Kimford J Meador, Gus A Baker, Nancy Browning, Morris J Cohen, Rebecca L Bromley, Jill Clayton-Smith, Laura A Kalayjian, Andres Kanner, Joyce D Liporace, Page B Pennell, Michael Privitera, David W Loring, for the NEAD Study Group. Foetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study Lancet Neurol 2013;12:244-52.
116. Alsfouk, B. A., Almarzouqi, M. R., Alsfouk, A. A., Alageel, S., & Alsemari, A. (2021). Antiseizure medications use during pregnancy and congenital malformations: a retrospective study in Saudi Arabia. Saudi Pharmaceutical Journal, 29(9), 939-945.
117. 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.
118. Liu, A., Akimova, E. T., Ding, X., Jukarainen, S., Vartiainen, P., Kiiskinen, T., ... & Ganna, A. (2024). Evidence from Finland and Sweden on the relationship between early-life diseases and lifetime childlessness in men and women. Nature Human Behaviour, 8(2), 276-287.
119. Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009;50:1237-46.
120. Practice Guideline From the AAN, AES, and SMFM, Pack, A. M., Oskoui, M., Roberson, S. W., Donley, D. K., French, J., ... & Keezer, M. R. (2025). Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication. Epilepsy Currents, 15357597241258514.
121. Hiilesma VK, Bardy A, Teramo K. Obstetric outcome in woman with epilepsy. Am J Obstet Gynecol 1985;152:499-504.
122. Wide K, Winbladh B, Tomson T, Sarz-Zimmer K, Berggren E. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. Dev Med Child Neurol 2000;42:87-92.

123. Al Bunyan M, Abu Talib Z. Outcome of pregnancies in epileptic woman: a study in Saudi Arabia. Seizure 1999;8:26-29.
124. Alsfouk, B. A., Almarzouqi, M. R., Alageel, S., Alsfouk, A. A., & Alsemari, A. (2022). Patterns of antiseizure medication prescription in pregnancy and maternal complications in women with epilepsy: a retrospective study in Saudi Arabia. Saudi Pharmaceutical Journal, 30(3), 205-211.
125. Katz O, Levy A, Wiznitzer A, Sheiner E. Pregnancy and perinatal outcome in epileptic women:a population-based study. J Matern Foetal Neonatal Med 2006 Jan;19(1):21-25.
126. Hébert, J., Iyengar, Y., Ng, S., Liao, J., Snelgrove, J. W., & Bui, E. (2024). Obstetrical outcomes of patients with epilepsy in a Canadian tertiary care center (2014–2020). Canadian Journal of Neurological Sciences, 51(3), 397-403.
127. Pennell PB. EURAP Outcomes for Seizure Control During Pregnancy: Useful and Encouraging Data. Epilepsy Curr 2006 Nov; 6(6): 186-88.
128. Kelly, B. (2025). The modern psychiatrist's guide to contemporary practice: discussion, dissent, and debate in mental health care (p. 272). Taylor & Francis.
129. Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia 2012;53(5):85-88.
130. Hungarian Central Statistical Office. Demographic yearbook. Budapest: Hungarian Central Statistical Office; 2016.
131. Perucca, P., Battino, D., Bromley, R., Chen, L., Craig, J., Hernandez-Diaz, S., ... & Tomson, T. (2025). Epilepsy-pregnancy registries: An update. Epilepsia, 66(1), 47-59.
132. Yoldemir, T. (2025). Perimenopausal combined hormonal contraception: focus on sexual function. Climacteric, 28(1), 15-20.
133. Vanya, M., Devosa, I., Pásztor, N., et al. (2016). Determinants of the reliable contraceptive use: A nationwide cross-sectional survey in Hungary. Endocrine Abstracts, 41, EP676.
134. Thiel de Bocanegra, H., Chang, R., Menz, M., et al. (2013). Postpartum contraception in publicly-funded programs and interpregnancy intervals. Obstetrics & Gynecology, 122(2), 296–303.
135. Ukah, C. E., Orock-Benem, V. T., Shei, C. M., Ngeha, C. N., Nangue, F. D. T., Dang, S. Z., ... & Ekeme, M. (2024). Prevalence and determinants of repeat pregnancy among adolescent girls in selected health areas of the Limbe Health District of Cameroon: A community-based cross-sectional study.

136. Powers, M. E., Takagishi, J., Alderman, E. M., Chung, R. J., Grubb, L. K., Lee, J., ... & Vanderbilt, D. L. (2021). Care of adolescent parents and their children. Pediatrics, 147(5).
137. Labbok, M. H. (2015). Postpartum sexuality and the lactational amenorrhea method for contraception. Clinical Obstetrics and Gynecology, 58(4), 915–927.
138. Calik-Ksepka, A., Stradczuk, M., Czarnecka, K., Grymowicz, M., & Smolarczyk, R. (2022). Lactational amenorrhea: neuroendocrine pathways controlling fertility and bone turnover. International journal of molecular sciences, 23(3), 1633.
139. Van der Wijden, C., & Manion, C. (2015). Lactational amenorrhoea method for family planning. Cochrane Database of Systematic Reviews, 12, CD001329.
140. Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists. (2017). FSRH guideline: Contraception after pregnancy. Retrieved January 25, 2017, from https://www.fsrh.org/standards-and-guidance/documents/contraception-after-pregnancy-guideline-january-2017
141. Yamaguchi, M., Motohara, T., Ohba, T., & Kondoh, E. (2025). Vascular Retained Products of Conception Following Delivery: Efficacy of Estrogen–Progestogen Therapy. Journal of Clinical Ultrasound.
142. Sok, C., Sanders, J. N., Saltzman, H. M., et al. (2016). Sexual behavior, satisfaction, and contraceptive use among postpartum women. Journal of Midwifery & Women's Health, 61(2), 158–165.
143. McDonald, E. A., & Brown, S. J. (2013). Does method of birth make a difference to when women resume sex after childbirth? BJOG: An International Journal of Obstetrics & Gynaecology, 120(7), 823–830.
144. Yee, L. M., Kaimal, A. J., Nakagawa, S., et al. (2013). Predictors of postpartum sexual activity and function in a diverse population of women. Journal of Midwifery & Women's Health, 58(6), 654–661.
145. Centers for Disease Control and Prevention. (2016). Breastfeeding report card. Atlanta, GA: CDC.
146. Sámano, R., Chico-Barba, G., Martínez-Rojano, H., Mendoza-Flores, M. E., Hernández-Trejo, M., Hernández-Chávez, C., ... & López-Ocampo, A. (2025). Association of Pre-and Gestational Conditions and Barriers to Breastfeeding with Exclusive Breastfeeding Practices. Nutrients, 17(14), 2309.
147. Australian Institute of Health and Welfare. (2011). 2010 Australian national infant feeding survey: Indicator results. Canberra, ACT: AIHW.

148. NHS Digital. (2012). Infant feeding survey – UK 2010. Retrieved November 20, 2012, from http://digital.nhs.uk/catalogue/PUB08694
149. Kozinszky, Z., Boda, K., & Bártfai, G. (2001). Determinants of abortion among women undergoing artificial termination of pregnancy. European Journal of Contraception & Reproductive Health Care, 6(3), 145–152.
150. Potter, J. E., Hubert, C., & White, K. (2017). The availability and use of postpartum LARC in Mexico and among Hispanics in the United States. Maternal and Child Health Journal, 21(9), 1744–1752.
151. Cleland, J., Shah, I. H., & Benova, L. (2015). A fresh look at the level of unmet need for family planning in the postpartum period, its causes and program implications. International Perspectives on Sexual and Reproductive Health, 41(3), 155–162.
152. Smith, M., McCool-Myers, M., & Kottke, M. J. (2021). Analysis of postpartum uptake of long-acting reversible contraceptives before and after implementation of Medicaid reimbursement policy. Maternal and Child Health Journal, 25(9), 1361-1368.
153. Loewenberg Weisband, Y., Keder, L. M., Keim, S. A., et al. (2017). Postpartum intentions on contraception use and method choice among breastfeeding women attending a university hospital in Ohio: A cross-sectional study. Reproductive Health, 14(1), 45.
154. Hathaway, M., Torres, L., Vollett-Krech, J., et al. (2014). Increasing LARC utilization: Any woman, any place, any time. Clinical Obstetrics and Gynecology, 57(4), 718–730.
155. Cameron, S. (2014). Postabortal and postpartum contraception. Best Practice & Research Clinical Obstetrics & Gynaecology, 28(6), 871–880.
156. Heller, R., Cameron, S., Briggs, R., et al. (2016). Postpartum contraception: A missed opportunity to prevent unintended pregnancy and short interpregnancy intervals. Journal of Family Planning and Reproductive Health Care, 42(2), 93–98.
157. Devosa, I., Németh, G., & Griechisch, E. (2025). A mesterséges intelligencia nyújtotta lehetőségek a prevenciós munkában 2024 első félévében. Magyar Nőorvosok Lapja, 88(1).
158. Finkelsztejn A, Brooks JB, Paschoal FM Jr, Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG. 2011 Jun; 118(7):790-7.
159. Corsellis JA, Goldberg GJ, Norton AR. Limbic encephalitis and its association with carcinoma. Brain. 1968 91(3):481-96.

160. Hu, X., & Cheng, S. (2024). The role of immunoglobulin in cerebrospinal fluid on the differential diagnosis of autoimmune encephalitis and viral encephalitis in children. BMC pediatrics, 24(1), 386.
161. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481-94.
162. Sanvito, F., Pichiecchio, A., Paoletti, M., Rebella, G., Resaz, M., Benedetti, L., ... & Roccatagliata, L. (2024). Autoimmune encephalitis: what the radiologist needs to know. Neuroradiology, 66(5), 653-675.
163. Alamowitch S, Graus F, Uchuya M, et al. Limbic encephalitis and small cell lung cancer. Clinical and immunological features. Brain 1997;120:923-28.
164. Norrito, R. L., Puleo, M. G., Pintus, C., Basso, M. G., Rizzo, G., Di Chiara, T., ... & Tuttolomondo, A. (2024). Paraneoplastic cerebellar degeneration associated with breast cancer: a case report and a narrative review. Brain Sciences, 14(2), 176.
165. Anderson NE, Barber PA. Limbic encephalitis – a review. J Clin Neurosci 2008; 15:961-71.
166. Kotteti, A. K., Chelvakumar, E. G., Sundaram, R. W., Radhakrishnan, K., Subbiah, A., Wilson, R., & S IV, A. (2024). Varied Clinical Features and Outcomes of Autoimmune Encephalitis: A Retrospective Case Series. Cureus, 16(12).
167. Vitaliani R, Mason W, Ances B, et al. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005; 3:58:59.
168. Graus, F. (2024). 40 years of autoantibody research in paraneoplastic neurological syndromes. Revue Neurologique.
169. Nelson JL. Maternal–foetal immunology and autoimmune disease. Is some autoimmune disease auto-alloimmune or allo-autoimmune? Arthritis & Rheumatism 1996; 39(2):191-94.
170. Nelson, J. L., & Lambert, N. C. (2025). The when, what, and where of naturally-acquired microchimerism. In Seminars in Immunopathology (Vol. 47, No. 1, pp. 1-21). Springer Berlin Heidelberg.
171. Ramagopalan SV, Herrera BM, Valdar W, et al. No effect of birth weight on the risk of multiple sclerosis. A population-based study. Neuroepidemiology 2008;31:181-4.
172. Holz, A., Obi, N., Ahrens, W., Berger, K., Bohn, B., Brenner, H., ... & Becher, H. (2024). Childhood and adolescence factors and multiple sclerosis: results from the German National Cohort (NAKO). BMC neurology, 24(1), 123.

173. Dahl J, Myhr KM, Daltveit AK, Gilhus NE. Pregnancy, delivery and birth outcome in different stages of maternal multiple sclerosis. J Neurol 2008;255:623-7.
174. Rahmati, S., Galavi, Z., Kavyani, B., Arshadi, H., Geerts, J., & Sharifi, H. (2024). Maternal and neonatal outcomes in pregnant women with multiple sclerosis disease: A systematic review and meta-analysis. Midwifery, 104004.
175. Chen YH, Lin HI, Lin HC. Does multiple sclerosis increase risk of adverse pregnancy outcomes? A population based study. Mult Scler 2009; 15:606-12.
176. Bast, N., Dost-Kovalsky, K., Haben, S., Friedmann, N., Witt, L., Oganowski, T., ... & Hellwig, K. (2025). Impact of disease-modifying therapies on pregnancy outcomes in multiple sclerosis: a prospective cohort study from the German multiple sclerosis and pregnancy registry. The Lancet Regional Health–Europe, 48.
177. Ehrenstein V, Pedersen L, Holsteen V, Larsen H, Rothman KJ, Sørensen HT. Postterm delivery and risk for epilepsy in childhood. Pediatrics. 2007 Mar;119(3):554-61.
178. Yerby MS. Contraception, pregnancy and lactation in women with epilepsy. Baillieres Clin Neurol 1996;5:887-908.
179. Haseitel, M. A., & Hardaman, C. G. (2021). Contraception in epileptic women. Medicina, 81(1), 62-68.
180. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community based, prospective controlled study of obstetric and neonatal outcome of 179 pregnancies in woman with epilepsy. Epilepsia 2006;47:186-192.
181. Berry-Noronha, A., Manoleehakul, P., Rottler, A., McGuiness, G., Chen, Z., Kuhn, R., ... & Perucca, P. (2025). Risk of Adverse Pregnancy Outcomes Associated With Antiseizure Medications and Their Indications: A Systematic Review and Meta-Analysis. Neurology, 104(3), e210233.
182. Samrén EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily E, Granström ML, Meinardi H, Grobbee DE, Hofman A, Janz D, Lindhout D. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia 1997;38:981-90.
183. Miller, I. O., & Sotero de Menezes, M. A. (2022). SCN1A seizure disorders.
184. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM. The teratogenicity of anticonvulsant drugs. N Engl J Med. 2001;344:1132-8.
185. Válóczy, R. (2024). Biológiai eseményekhez társuló epilepszia vizsgálata - Doctoral dissertation, Debreceni Egyetem, Hungary.

Appendix

Supplement 1. The summary of teratogenicity of various AEDs

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Samrén (1999)	Retrospective cohort	376	3.7	RR: 2.6 (1.4–5.0)
Kaneko (1999)	Prospective	158	5.7	OR: 1.9
Holmes (2001)	Prospective	58	5.2	OR: 3.0 (0.6–16)
Matalon (2002)	Meta-analysis	795	5.5	OR: 2.36 (1.62–3.43)
Wide (2004)	Retrospective	703	4.0	NA
Artama (2005)	Retrospective	805	4.0	OR: 1.27 (0.7–2.23)
Vajda (2006)	Prospective and retrospective	155	3.8	p = 1.0000
Morrow (2006)	Prospective	900	2.2	OR: 1.0
Hernandez-Diaz (2007)	Prospective	873	2.5 (1.6–3.7)	OR: 1.6 (0.9–2.8)

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Vajda (2007)	Prospective	234	3.0	OR: 0.82 (0.21–3.26)
Meador (2008)	Systematic review and meta-analysis	4411	4.6	NA
Montouris (2003)	Prospective and retrospective	17	5.9	NA
Morrow (2006)	Prospective	31	3.2 (0.6–16.2)	OR: 1.33 (0.17–10.20)
Vajda (2007)	Prospective	11	0	NA
Holmes (2008)	Prospective	127	0.8 (0.039– 3.8)[†]	NA
Morrow (2006)	Prospective	647	3.2 (2.1–4.9)	OR: 1.44 (0.77–2.67) RR: 0.92 (0.41–2.05)
Vajda (2006)	Prospective and retrospective	61	0	p = 0.3960
Vajda (2007)	Prospective	146	1.4	OR: 0.37 (0.06–2.26)

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Meador (2008)	Systematic review and meta-analysis	1337	2.9 (2.00–3.82)	NA
Holmes (2008)	Prospective	684	2.80 (1.7–4.3)	RR: 1.4 (0.9 – 2.3)
Hunt (2009)	Prospective	1151	2.4 (1.7– 3.5)	NA
Long (2003)	Case series	3	0	NA
Ten Berg (2005)	Prospective	2	0	NA
Morrow (2006)	Prospective	22	0	NA
Hunt (2006)	Prospective	39	0	NA
Holmes (2008)	Prospective	197	2.0 (0.65–4.8)[†]	NA
Samrén (1999)	Retrospective	172	2.9	RR: 2.0 (0.8–5.3)
Holmes (2001)	Prospective	64	4.7	OR: 2.7 (0.6–16.4)

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Holmes (2004)	Prospective	77	6.5 (2.1–14.5)	RR: 4.2 (1.5–9.4)
Meador (2008)	Systematic review and meta-analysis	945	4.9 (3.22–6.59)	NA
Samrén (1999)	Retrospective	151	0.7	RR: 0.5 (0.1–3.4)
Holmes (2001)	Prospective	87	3.4	OR: 1.9 (0.3–9.2)
Artama (2005)	Retrospective	38	2.6	OR: 0.95 (0.02–6.11)
Morrow (2006)	Prospective	82	3.7 (1.3–10.2)	OR: 1.64 (0.48–5.62)
Vajda (2006)	Prospective and retrospective	17	5.9	p = 0.5113
Vajda (2007)	Prospective	31	3.2	OR: 0.90 (0.09–8.88)
Meador (2008)	Systematic review and meta-analysis	1198	7.4 (3.60–11.11)	NA

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Holmes (2008)	Prospective	390	2.6 (1.2–4.5)[†]	NA
Morrow (2006)	Prospective	28	2.0	OR: 7.1 (2.0–22.6)
Vajda (2007)	Prospective	15	0	NA
Ornoy (2008)[‡]	Prospective	29	3.5	NA
Hunt (2008)	Prospective UK Epilepsy and Pregnancy Register	70	4.8 (1.7–13.3)	NA
Holmes (2008)	Prospective	197	4. (1.9–7.6)[†]	NA
Kaneko (1999)	Prospective	81	11.1	OR: 4
Samrén (1999)	Retrospective	158	5.7	RR: 4.1 (1.9–8.8)
Wide (2004)	Retrospective	268	9.7	NA
Artama (2005)	Retrospective	263	10.7	OR: 4.18 (2.31–7.57)

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)
Morrow (2006)	Prospective	715	6.2 (4.6–8.2)	OR: 2.78 (1.62–4.76) RR: 2.52 (1.17–5.44)
Vajda (2006)	Prospective and retrospective	113	16.8	p = 0.0262
Vajda (2007)	Prospective	166	13.3	OR: 4.07 (1.18–14.0)
Meador (2008)	Systematic review and meta-analysis	2097	10.7 (8.16–13.29)	NA