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

Ph.D. Thesis Summary

Dr. Melinda Vanya

Supervisor:

Dr. Iván Devosa, Ph.D.

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ABBREVIATIONS

AED – Antiepileptic drug

ART – Assisted reproductive 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 therapy

EDSS – Expanded Disability Status Scale

ICD-10 – International Classification of Diseases, 10th Revision

IFN – Interferon

IL – Interleukin

ILAE – International League Against Epilepsy

HLA – Human leukocyte antigen

LARC – Long-acting reversible contraception

LAM – Lactational amenorrhea

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 – Pregnancy in Multiple Sclerosis (international study)

PRISMS – Prevention of Relapses and Disability by Interferon β-1a (international study)

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 cell

TSH – Thyroid-stimulating hormone

UV-B – Ultraviolet-B radiation

VPA – Valproic acid

WWE – Women with epilepsy

LIST OF PUBLICATIONS RELATED TO THE THESIS

I. Publication

Vanya, M., Nyári, T., Bencsik, K., & Bártfai, G. (2014). Pregnancy and perinatal outcomes in women with multiple sclerosis: a retrospective case-control study in Southern Hungary. Journal of Maternal-Fetal & Neonatal Medicine, 27(6), 577–581.

II. Publication

Vanya, M., Árva-Nagy, N., Szili, K., Szok, D., & Bártfai, G. (2015). Effects of maternal epilepsy and antiepileptic therapy during pregnancy. Ideggyógyászati Szemle, 68(3–4), 105–112.

III. Publication

Vanya, M., Devosa, I., Barabás, K., Bártfai, G., & Kozinszky, Z. (2018). Contraceptive method choice at 6–8 weeks postpartum in Southeastern Hungary. European Journal of Contraception and Reproductive Health Care, 23(1), 52–57.

INTRODUCTION

Neuropsychiatric disorders have a significant impact on reproductive health, pregnancy outcomes, and fetal development. These conditions present serious interdisciplinary challenges in both clinical care and research. Among them, multiple sclerosis (MS) and epilepsy deserve particular attention, as they can adversely affect the health of both mother and child. In women of reproductive age, conscious family planning is of utmost importance, which includes the selection and consistent use of appropriate contraceptive methods. Multiple sclerosis primarily affects women of reproductive age; therefore, pregnancy management carries major clinical relevance. The unpredictable course of the disease—characterized by alternating relapses and remissions—complicates both the management of pregnancy and the decision-making regarding disease-modifying therapies. Current data suggest that pregnancy exerts a stabilizing effect on MS, with a reduced relapse rate especially in the third trimester. However, in the postpartum period, the risk of disease relapse increases again. The exact mechanisms underlying MS-related complications, such as miscarriage or intrauterine fetal death, remain unclear. Epilepsy poses further challenges, as antiepileptic drugs (AEDs) may adversely influence pregnancy outcomes, the incidence of congenital malformations, and the neurological development of the newborn. Although therapeutic options are constantly evolving, pregnancies in women with epilepsy require individualized clinical strategies. During AED therapy, a delicate balance must be maintained between maternal seizure control and fetal safety. Regular monitoring of drug levels and dose adjustments are essential during pregnancy, considering the physiological changes that affect drug metabolism. A deeper understanding of these interactions may contribute to the development of targeted preventive strategies and early intervention programs, thereby improving the long-term developmental outcomes of children at risk.

I. MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of disability among young

adults. In Western countries, it affects about 1 in 1,000 people, with an estimated 2.5 million patients worldwide. In Hungary, the prevalence is approximately 65 per 100,000 inhabitants. Relapsing–remitting form (RRMS): about 85% of cases. Characterized by periodic neurological relapses followed by full or partial remission. Secondary progressive form (SPMS): about 90% of RRMS patients convert within 25 years. Continuous neurological decline is observed. Primary progressive form (PPMS): about 15% of cases. Marked by gradual, continuous deterioration without clear relapses. MS is a single disease that manifests in different phenotypes. Its hallmarks are inflammation, demyelination, and axonal damage. Oligodendrocytes (responsible for maintaining the myelin sheath) are attacked by T-cells and activated macrophages/microglia. Two main pathological changes can be distinguished: focal demyelinated plaques and diffuse brain damage. As the disease progresses, diffuse damage dominates, leading to atrophy. On average, within 20 years of diagnosis, most patients require walking aids. Life expectancy is about 10 years shorter compared to the general population. Etiology: Both genetic and environmental factors play a role: genetics: carriage of the HLA-DRB1*1501 allele significantly increases risk. Environmental: migration studies show that relocation to high-prevalence regions before age 15 increases risk. Epstein–Barr virus: history of mononucleosis increases risk ≥20-fold.
- Vitamin D deficiency: MS is more common at higher latitudes; lack of UV-B radiation may contribute to pathogenesis. Diagnosis: there is no single specific diagnostic test; diagnosis is based on history and clinical presentation. Criteria include: - Spatial dissemination (≥2 different CNS regions affected). Temporal dissemination (≥2 relapses). Diagnostic criteria: Additional examinations: MRI, evoked potentials, cerebrospinal fluid oligoclonal bands. Differential diagnoses: ADEM, infections, SLE, sarcoidosis, NMO, tumors. Immunological aspects and pregnancy: hormonal changes influence autoimmune processes. During pregnancy, estrogen and progesterone exert anti-inflammatory effects, with Th2-dominance prevailing. Postpartum, Th1-dominance returns, increasing relapse risk. Key contributors include regulatory T-cells, NK cells, alpha-fetoprotein, and IL-10. MS often manifests after childbirth. During pregnancy—especially in the third trimester—the number of relapses decreases. Postpartum, however, relapse frequency increases again (25–50%). Evidence on disease-modifying therapies (DMDs) remains controversial, but no definitive teratogenic effects have been proven.

II. EPILEPSY AND PERINATAL OUTCOMES

Epilepsy is among the most common chronic neurological disorders, with a prevalence of 0.5–0.7% in the European Union and 0.3–0.5% among pregnant women. In childhood and adolescence, congenital, developmental, and genetic factors are the most frequent causes. However, epilepsy can develop at any age due to head trauma, central nervous system infection, or tumor. Diagnosis of epilepsy is based on medical history, clinical examination, and EEG findings. According to the International League Against Epilepsy (ILAE) classification:

- Primary (idiopathic) epilepsy: genetically determined syndromes with characteristic clinical and EEG features.

- Secondary (symptomatic) epilepsy: linked to a known cause, such as trauma or tumor.

- Seizure types and syndromes are classified according to the latest ILAE recommendations, distinguishing between focal and generalized onset.

Management in women planning pregnancy:

Treatment should be optimized prior to conception:
- Close collaboration between neurologist and obstetrician-gynecologist.
- Selection of an AED that provides seizure control at the lowest effective dose.
- Avoidance of valproic acid whenever possible.
- Preference for monotherapy.
- Mandatory folic acid supplementation.

Risks of AED use during pregnancy:
- Major congenital malformations (MCM) are the primary concern, and AED exposure may also affect long-term cognitive development of the child.
- The first trimester carries the highest risk.
- Teratogenic effects are dose-dependent.
- Valproic acid is associated with the greatest risk.
- Folic acid supplementation significantly reduces the incidence of neural tube defects.

Breastfeeding:
Antiepileptic drugs pass into breast milk, and their concentration is generally proportional

to maternal plasma levels. However, neonatal drug-metabolizing systems are immature. Despite this, international literature consistently recommends encouraging women with epilepsy to breastfeed, as the benefits outweigh potential risks.

Outcomes:
- About 90% of women with epilepsy deliver healthy babies without complications.
- However, higher rates of miscarriage, preterm birth, intrauterine growth restriction, and low birth weight are observed.
- Maternal complications are more common, including hypertension, gestational diabetes, and, rarely, severe intracranial hemorrhage.

Seizure course during pregnancy:
- About 60% of women remain seizure-free during pregnancy.
- Hormonal and metabolic changes affect seizure frequency.
- Seizures are more frequent in the third trimester.

III. CHOICE OF CONTRACEPTIVE METHOD

In 2015, the total fertility rate in Hungary was 1.45, which was below the European Union average. Although Hungarian women plan an average of 2.4 children, the majority eventually have only one. Contributing factors include career building, financial insecurity, and family circumstances. In 2016, approximately 20% of pregnancies ended in termination. At the same time, postponement of childbearing has become increasingly common, making the choice of an optimal contraceptive strategy more difficult.

At older maternal ages, the risks associated with combined hormonal methods increase. Access to effective, modern contraceptive methods is often limited. Sexual behavior and childbearing intentions are strongly age-dependent. Long-acting reversible contraceptives (LARC), such as intrauterine devices (IUDs) and implants, are safe and highly effective, particularly in the postpartum period, yet their use in Hungary remains low (5.9%). The 6–8 week postpartum period is particularly critical for initiating reliable contraception, especially among high-risk groups. Lactational amenorrhea (LAM), which relies on ovulation suppression, can be an effective temporary method during the puerperium if exclusive breastfeeding is maintained. Women should be counseled on contraceptive options that can be initiated immediately postpartum, including:intrauterine device (IUD), levonorgestrel-

releasing intrauterine system (LNG-IUS), progestogen implant. For optimal results, these methods are recommended to be introduced within 21 days postpartum, regardless of breastfeeding status. Determinants of contraceptive effectiveness: sociodemographic background, economic situation, sexual and reproductive history, breastfeeding practices. The aim of our study was to explore how these factors influence postpartum contraceptive behavior, with special focus on the use of effective methods and lactational amenorrhea (LAM).

OBJECTIVES OF THE THESIS

The aim of this dissertation was to explore the effects of neuropsychiatric disorders—primarily multiple sclerosis and epilepsy—on reproductive health, as well as to investigate postpartum contraceptive practices. Our specific objectives were as follows:

1. To analyze the effects of multiple sclerosis on pregnancy, childbirth, and neonatal outcomes (Publication I).

2. To examine the impact of epilepsy and antiepileptic therapy during pregnancy and the perinatal period (Publication II).

3. To explore trends in postpartum contraceptive method choice, with special attention to the role of effective methods and lactational amenorrhea (Publication III).

The purpose of these studies was to provide new data contributing to improvements in clinical care, reduction of risks, and support for clinical decision-making and patient education.

MATERIALS AND METHODS

Multiple sclerosis (MS)

Our study included 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 care at the Department of Neurology, University of Szeged, between January 1, 1998, and December 31, 2012. Of the 102 patients, 65 did not receive disease-modifying therapy (DMD). Since DMD may potentially cause pregnancy complications, women requiring DMD due to disease progression were excluded from the study. Control group: 65 age-matched pregnant women without MS or other

neuroimmunological diseases. Both groups were further divided into primigravida and multigravida subgroups.

Epilepsy

In this retrospective case-control study, we analyzed the data of 91 pregnant women with epilepsy who were followed at the University of Szeged between December 31, 2000, and March 31, 2014. Participants were divided into three subgroups: untreated, monotherapy, polytherapy. Control group: 182 pregnant women without epilepsy or other neuropsychiatric disorders.

Contraception

Initially, 1875 women were approached for participation. 611 declined, and 21 were excluded (under 18 years of age, illiterate, or non-native Hungarian speakers). The final sample included 599 women (response rate: 67%), who completed the questionnaire at 6–8 weeks postpartum.

Variables examined

Sociodemographic data: educational level, marital status, residence, employment. Obstetric data: pregnancy complications, mode of delivery, gestational age, neonatal weight and length, head circumference, breastfeeding. MS-specific data: disease subtype, disease duration, EDSS score. Epilepsy-specific data: AED type and dose, seizure occurrence by trimester, seizure type (according to ILAE), incidence of major congenital malformations (MCM). Contraception-specific data: predictors of effective method choice (LAM + hormonal, IUD, sterilization).

Statistical analysis

Data were analyzed using SPSS version 20. Categorical variables: χ^2 test, Fisher's exact test, odds ratio (95% CI). Continuous variables: two-sample t-test, ANOVA. Logistic regression: stepwise method. Significance level: $p < 0.05$.

Ethical approval

The studies were approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged, in accordance with the Declaration of Helsinki. Approval numbers:

- MS: 194/2010

- Epilepsy: 3136/2012

- Contraception: 125/2011

RESULTS

I. Multiple sclerosis (MS)

Between 2000 and 2012, we followed 102 pregnancies in women with MS. Sixty-five women did not receive disease-modifying therapy. General characteristics: At MS diagnosis, mean age was 26.3 years among primigravidae and 27.7 years among multigravidae. At first pregnancy, mean age was 29.6 years for primigravidae and 25.1 years for multigravidae. EDSS scores did not differ significantly between groups. Marital status: The proportion of married women was significantly higher in the MS group (72.3% vs. 34.3%; $p < 0.001$). Hospitalization: Women with MS had longer hospital stays (33.8% vs. 0%; $p = 0.004$), mainly due to depression. Miscarriage and intrauterine death: Miscarriage frequency was significantly higher ($p < 0.001$), especially among multigravidae. Intrauterine fetal death occurred in 7.69% ($p = 0.035$). Perinatal outcomes: rates of preterm birth, post-term pregnancy, and high birth weight did not differ compared to controls. Twin pregnancies were more common in the MS group (4.6% vs. 0%). - Pregnancy termination: 27 elective, 1 for medical indication (MS progression).

II. Epilepsy

Maternal characteristics: Mean maternal age was similar between groups (29.4 years vs. 29.7 years). Obesity was more frequent among controls. Hypertension and preeclampsia were significantly more common in women with epilepsy ($p < 0.001$). Seizure occurrence: During pregnancy, 37% of women remained seizure-free. Distribution of seizures: 1st trimester 26%, 2nd trimester 25%, 3rd trimester 49%. During delivery: 5 cases (8.8%). Postpartum: 4 cases (7%). Obstetric outcomes: Miscarriage was more frequent in women with epilepsy (7% vs. 0%; $p = 0.001$). Vaginal delivery rate was lower (53.6% vs. 66%; $p = 0.001$). Cesarean

section rate was higher (45% vs. 34%; p = 0.022). Newborns of women with epilepsy had lower mean birth weight, length, head circumference, and chest circumference (p < 0.001). Antiepileptic drug therapy: 21% untreated, 33% monotherapy, 45% polytherapy. Most common agents: valproic acid, lamotrigine, carbamazepine. Major congenital malformations (MCM): Prevalence 7.7%, mostly associated with valproic acid (e.g., congenital heart defects, hypospadias, gastroschisis). Breastfeeding: Lower rates among women with epilepsy (75% vs. 100%).

III. Contraception

Maternal characteristics: Mean age 31–33 years. Sociodemographic factors: no significant differences by education, residence, or number of children. Breastfeeding and menstruation: Exclusive breastfeeding was associated with higher likelihood of using an effective method or LAM. Menstruation return: 28.9% among effective method users, 41.5% among condom users. Sexual activity: Prepartum contraceptive practice strongly predicted postpartum choice. The method used at first postpartum intercourse closely correlated with the choice at 6–8 weeks. Women using effective methods were more likely to be sexually active. Method choice: 49% of women were sexually active 6–8 weeks postpartum. 91.5% used some form of contraception: 22% condoms, 15.5% less effective methods, 40% LAM, 22.5% highly effective methods.- LARC use: Extremely low (4.8% IUD, 0% implant).

DISCUSSION

Pregnancies in women with multiple sclerosis and epilepsy are rare and require special attention. For successful outcomes, close collaboration between neurologists and obstetrician-gynecologists is essential, along with providing patients with accurate, evidence-based information.

Multiple sclerosis: In our study, women with MS showed a low rate of assisted reproductive technology (ART) use, suggesting that fertility is not significantly impaired in the early stages of the disease. By including a control group, we were able to eliminate potential bias. Women with MS were significantly more likely to experience prolonged hospitalization, mainly due to depression. Miscarriage and intrauterine fetal death rates were also higher, particularly in multigravidae, raising the possibility of cumulative adverse effects. The rate of cesarean section was also increased (p = 0.002), which may partly reflect physician caution. Twin pregnancies were also more frequent, although little data exist on the underlying reasons.

Neonatal outcomes—such as birth weight, gestational age, and congenital malformations—did not differ significantly, which is consistent with the findings of Ramagopalan.

Epilepsy: Women with epilepsy had higher rates of hypertension and preeclampsia, consistent with the findings of Bunyan. Seizure frequency increased during three periods: the first and second trimesters and around delivery, confirming observations made by Thomas. Rates of miscarriage and cesarean delivery were higher among women with epilepsy, suggesting that epilepsy itself may be considered an indirect indication in obstetric decision-making. Neonatal outcomes—including lower birth weight, length, and head circumference, as well as poorer Apgar scores and umbilical cord pH—were less favorable, although gestational age did not differ. Congenital malformations were primarily associated with valproic acid, particularly at high doses or in polytherapy, consistent with Holmes' findings on cardiac malformations. Folic acid supplementation remains a key preventive measure for neural tube defects. Breastfeeding rates were lower among women with epilepsy. Although AEDs pass into breast milk, exposure levels are lower than during intrauterine transplacental transfer.

Contraception: at 6–8 weeks postpartum, most women used some form of contraception, although LARC methods remained extremely underutilized (4.8%). Effective method choice was influenced by several factors: higher partner educational level, return of menstruation, and contraceptive practice prior to pregnancy and at first postpartum intercourse. Our findings emphasize the importance of improving health communication, increasing access to LARC methods, and expanding patient education.

NEW OBSERVATIONS AND RECOMMENDATIONS

1. Multiple sclerosis and pregnancy outcomes: in women with MS, miscarriages and intrauterine fetal deaths were significantly more frequent among multigravidae, suggesting a possible cumulative adverse effect. Recommendation: Multigravida women with MS require intensified prenatal care. The higher prevalence of depression in pregnant women with MS justifies incorporating psychological screening and support into routine care.

2. Epilepsy and pregnancy: higher rates of hypertension and preeclampsia were observed in women with epilepsy → cardiovascular risk should be closely monitored. Increased seizure frequency in the third trimester → regular monitoring of drug levels and appropriate dose

adjustments are necessary. Valproic acid use should be avoided during pregnancy due to its considerable teratogenic risk.

3. Contraceptive practice: the use of LARC methods remained extremely low (4.8%). Partner's educational level had a stronger influence on effective method choice than the mother's own educational level. Despite the widespread use of LAM, women were aware that it is not the most reliable method. Recommendation: Modern communication strategies (social media, digital counseling, AI-based tools) are needed to effectively reach younger generations.

4. General clinical conclusions: multidisciplinary collaboration is required, involving obstetricians, neurologists, psychiatrists, geneticists, and pediatricians. Implementation of standardized clinical guidelines and targeted patient education is recommended. Prospective studies are needed to clarify the associations between neuropsychiatric disorders, pharmacological treatments, and offspring outcomes. Improving access to reliable postpartum contraception is essential to reduce unplanned pregnancies.

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LIMITATIONS OF THE STUDY

Our study has several limitations that may affect the generalizability of the results: due to gaps in data collection, detailed information was not available regarding maternal smoking, use of psychoactive substances, folic acid intake, or the administration of antidepressants during pregnancy. Data on breastfeeding among women with epilepsy were also incomplete, which could have provided valuable supplementary information for evaluating maternal and neonatal outcomes. These limitations restrict the comprehensive interpretation of the results but highlight the need for further prospective studies with larger sample sizes to provide more accurate insights.