

Epilepsy in Pregnancy: An Integrative, Life-Course Management Framework for Optimising Maternal and Fetal Outcomes

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Abstract

Women with epilepsy (WWE) account for 0.3–0.7 % of all pregnancies, yet their care remains one of obstetrics' most complex balancing acts. Clinicians must juggle maternal seizure control, teratogenic risks of anti-seizure medications (ASMs), rapidly changing drug pharmacokinetics, and heightened obstetric morbidity—all while supporting reproductive autonomy. This narrative review synthesises high-quality literature published between January 2020 and June 2025 alongside major guideline updates from the American Academy of Neurology (AAN), American Epilepsy Society (AES), International League Against Epilepsy (ILAE) and European regulators. We examine: (1) pre-conception counselling, folate optimisation and ASM selection; (2) mechanistic and epidemiologic data on teratogenicity and neuro-developmental sequelae; (3) pregnancy-induced pharmacokinetic shifts and therapeutic-drug-monitoring (TDM) algorithms; (4) seizure-, medication- and obstetric-related maternal-fetal morbidities including SUDEP; (5) intrapartum and postpartum management, breastfeeding and contraception; and (6) emerging precision-dosing and digital-monitoring strategies. Evidence confirms that high-dose folic acid (≥ 1 mg/day) begun pre-conception, coupled with avoidance of valproate and vigilant TDM of lamotrigine or levetiracetam, reduces major congenital-malformation (MCM) rates to near-background levels. Multinational cohort data show WWE still face a 1.4-fold rise in severe maternal morbidity and a 1.5-fold rise in neonatal morbidity versus controls, underlining the need for multidisciplinary, guideline-aligned care. Future research priorities include prospective registries linking ASM serum concentrations to neuro-developmental outcomes, genotype-guided dosing platforms, and digital seizure-prediction tools to mitigate SUDEP.

Introduction

Epilepsy affects an estimated 65 million people worldwide; roughly one half are women, and one in every 200 pregnancies occurs in a woman taking long-term ASMs. Advances in pharmacology and perinatal medicine have reduced, but not eliminated, epilepsy-related risks. Valproate's teratogenicity remains the benchmark cautionary tale: up to 10 % MCM rate and 30–40 % neuro-developmental impairment are reported after in-utero exposure. Regulatory bodies therefore now restrict or ban valproate use in women of reproductive age unless no alternative exists. Meanwhile, newer agents such as lamotrigine (LTG) and levetiracetam (LEV) offer lower malformation rates but demand aggressive dose titration because pregnancy accelerates their clearance.

Beyond drug teratogenesis, WWE face higher obstetric complications—preeclampsia, haemorrhage, venous thrombo-embolism—and elevated mortality, with uncontrolled generalised tonic-clonic seizures (GTCS) the strongest predictor of SUDEP. A 2024 multinational cohort of 4.5 million pregnancies reported a 48 % increase in severe neonatal morbidity and a 20 % rise in perinatal mortality among WWE, independent of ASM exposure. Optimal outcomes therefore hinge on a continuum of care that begins before conception and extends into the postpartum period.

This review collates recent evidence to craft an integrative management framework that can be operationalised in both resource-rich and resource-limited settings.

Methodology

Using PRISMA-Lite methods, we searched PubMed, Scopus and Google Scholar (January 2020 – June 2025) for English-language articles combining epilepsy, pregnancy, antiseizure medication, teratogenicity, folic acid, therapeutic drug monitoring, SUDEP, lamotrigine, and levetiracetam. Guideline statements from AAN/AES/SMFM (2024), RCOG (2022), ILAE (2023) and

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EMA/MHRA policy documents were included. After duplicate removal, 312 abstracts underwent screening; 110 high-quality RCTs, prospective cohorts, meta-analyses, and authoritative guidelines were synthesised. Heterogeneity in outcome definitions precluded meta-analysis; instead, weighted ranges and narrative integration were employed. Citations here reference representative, high-impact sources.

Discussion

1. Pre-Conception Phase

1.1 Folate Optimisation

High-dose folic acid (1–4 mg/day) at least three months pre-conception lowers neural-tube-defect (NTD) risk by up to 60 % compared with standard 0.4 mg doses, especially in ASM users . The Swiss Epilepsy League now recommends 1–3 mg daily for all women of child-bearing potential on ASMs, adjusting upward if taking enzyme-inducing drugs (EIDs) . Yet a 2025 ILAE podcast survey found only 41 % adherence among reproductive-aged women , highlighting gaps in counselling.

1.2 Teratogenicity-Aware ASM Selection

Pre-pregnancy seizure control remains the paramount predictor of maternal and fetal safety. Where seizure freedom has been maintained for ≥ 2 years, discussions of gradual taper may be reasonable; otherwise, monotherapy with lowest-effective dose of LTG or LEV is preferred. Valproate, phenobarbital and topiramate carry dose-related MCM and neuro-developmental risks and should be avoided when possible. EMA’s 2023 directive bans valproate for migraine or bipolar and severely restricts epilepsy use in pregnancy ; UK MHRA’s Pregnancy-Prevention Programme imposes similar safeguards .

1.3 Lifestyle and Comorbidity Screening

Women should receive counselling on sleep hygiene, alcohol avoidance, and seizure-trigger mitigation. Baseline labs (CBC, liver/kidney function) and psychiatric comorbidity screening refine risk assessment.

2. Teratogenic and Neuro-developmental Outcomes

A 2024 systematic review encompassing 62 000 ASM-exposed pregnancies confirmed valproate’s 10.4 % MCM rate but reported LTG (2.3 %) and LEV (2.0 %) rates approximating background risk . Long-term cognitive follow-up reveals subtle language delays with topiramate and polytherapy regimens, whereas LTG and LEV show no significant IQ decrement at age 6. Emerging data implicate prenatal ASM exposure—particularly polytherapy—in modestly increased odds of ASD/ADHD (pooled OR 1.3) , reinforcing monotherapy preference.

High-dose folic acid, long considered universally protective, may harbour an unexpected downside: a Scandinavian registry analysis linked maternal doses ≥ 4 mg/day to a 1.7-fold rise in childhood cancer among WWE . The absolute risk remains low (< 1 %), yet personalised dosing is warranted until mechanistic clarity emerges.

3. Pharmacokinetic Shifts and Therapeutic-Drug Monitoring

Pregnancy induces hormonal and physiological changes that accelerate hepatic glucuronidation and renal clearance, slashing LTG trough levels by up to 70 % and LEV levels by 50 % by third trimester.

Drug	Mean Clearance Increase	TDM Frequency	Dose-Adjustment Algorithm	Key Evidence
Lamotrigine	x3 by T3	Baseline, 4-weekly thereafter, 2 & 6 weeks postpartum	Increase dose 20–25 % per 20 % fall from pre-pregnancy trough	Population PK model 2025

Levetiracetam	x2 by T3	Baseline, thereafter	6-weekly	Increase dose when trough < 50 % baseline; anticipate rapid postpartum drop	Prospective cohort 2024
Valproate	Minimal	Not routinely needed; avoid use		N/A	
Topiramate	Moderate	Data sparse; monitor clinically		N/A	

Prospective TDM-guided dosing halves breakthrough seizure rates without exceeding pre-pregnancy serum concentrations. Digital adherence tools (smart blister packs) further cut missed-dose episodes.

4. Seizure Control, SUDEP and Obstetric Morbidity

4.1 Seizure Trajectory

Approximately 50 % of WWE experience unchanged seizure frequency, 25 % improve and 25 % worsen—largely those on LTG without dose escalation. Breakthrough GTCS elevate risks of trauma, hypoxia and precipitate preterm birth.

4.2 SUDEP

Uncontrolled nocturnal GTCS remain the dominant SUDEP risk factor. A 2024 Neurology study identified a 350-fold variance in SUDEP incidence based on seizure control metrics . Pregnancy-specific data are sparse, but registry reports suggest incidence of 1.3 per 10 000 pregnancies. Structured nocturnal supervision (partner, seizure alarms) and optimising ASM levels are advised. Yet knowledge gaps persist: 76 % of reproductive-aged women were unaware of SUDEP in a UK survey .

4.3 Maternal and Neonatal Complications

WWE display higher odds of severe preeclampsia, thrombo-embolism and postpartum haemorrhage. Neonates show elevated rates of preterm birth (10 %), SGA (12 %) and neonatal intensive-care admission (15 %) . ASM exposure amplifies these risks modestly (aOR 1.24), but seizure control remains the pivotal determinant.

5. Antenatal Surveillance

- First Trimester: Early viability scan, baseline TDM, and folate review. Offer chorionic-villus sampling or cell-free DNA based on maternal age and drug regimen.
- Anatomy Ultrasound (20–22 weeks): Particular focus on cardiac, neural tube and craniofacial structures; consider fetal echocardiography in valproate or topiramate exposure.
- Serial Growth Scans: 28, 32 and 36 weeks if on EIDs, polytherapy or with comorbid diabetes/hypertension.
- Vitamin K considerations: Enzyme-inducing ASM use warrants oral maternal vitamin K 20 mg daily from 36 weeks and 1 mg IM to neonate at birth.

6. Intrapartum Management

- Continuity of ASM: Ensure oral or IV dosing schedule maintained; LTG has a 6-hour half-life and missed doses precipitate seizures.
- Analgesia: Epidural is safe; however, ultrasound-guided placement can mitigate technical challenges in women on long-term steroids or with scoliosis.
- Seizure Protocol: IV lorazepam 4 mg for acute GTCS, escalate to phenytoin or levetiracetam loading if status epilepticus develops.
- Mode of Delivery: Vaginal birth is achievable in > 70 % when seizures controlled; elective caesarean considered for refractory seizures or obstetric indications.
- Foetal Monitoring: Continuous CTG; intrapartum hypoxia risks if maternal GTCS > 2 minutes.

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7. Post-partum, Lactation and Contraception

7.1 ASM Titration

LTG and LEV doses should return to pre-pregnancy levels within 2 weeks postpartum to avert toxicity. Rapid serum-level decline immediately after delivery predisposes to overshoot; TDM at days 3 and 14 guides adjustments.

7.2 Breastfeeding

Most ASMs—including LTG and LEV—are compatible with breastfeeding. LTG milk-to-plasma ratios average 0.4, with infant serum levels 20–50 % of maternal but rarely clinically significant . A 2024 meta-analysis noted no adverse cognitive outcomes at age 3. Monitor infants for sedation or rash.

7.3 Contraception and Inter-pregnancy Care

Enzyme-inducing ASMs reduce combined-oral-contraceptive efficacy; long-acting reversible contraception (IUD, implant) or levonorgestrel IUS is preferred. Valproate's paternal teratogenic risk warrants condom use and pre-conception counselling for treated men .

8. Emerging Directions and Research Gaps

1. Precision Dosing: Population-PK models embedded in electronic medical records now simulate trimester-specific LTG dosing, reducing time to therapeutic trough by 30 %.
2. Digital Seizure-Prediction Wearables: Early trials show 70 % sensitivity in flagging GTCS 30 minutes in advance, offering potential to avert hypoxia-related fetal compromise.
3. Gene–Drug Interaction Studies: UGT1A4 polymorphisms may predict LTG clearance variance; prospective validation is underway.
4. Longitudinal Neuro-developmental Registries: Linking maternal TDM data with child IQ and ASD metrics will disentangle drug vs. disease effects.

Conclusion

Management of epilepsy in pregnancy demands a life-course approach grounded in shared decision-making. Key pillars include: (1) high-dose folic acid and teratogenicity-informed ASM selection before conception; (2) aggressive, pharmacokinetically-guided dose adjustments—especially for LTG and LEV—through pregnancy and postpartum; (3) multidisciplinary obstetric, neurology and anaesthesia coordination to mitigate maternal and neonatal morbidities; and (4) sustained postpartum vigilance encompassing breastfeeding safety, SUDEP counselling and effective contraception. While contemporary strategies have narrowed the outcome gap, maternal mortality and neonatal morbidity remain higher than population baselines, signalling unfinished work. Priority research areas span precision dosing, digital seizure forecasting and long-term child neuro-development. Implementing guideline-concordant care universally—particularly in resource-limited settings—offers the greatest immediate leverage to safeguard both mother and child.

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