Chapter 1

Epidemiology of Women with Epilepsy

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Introduction

Key Points

- Epilepsy is common with a prevalence of between 3 and 10 cases per 1,000.
- There is a similar overall prevalence between males and females, although rare studies report a slightly higher lifetime incidence in males (1 of every 21 males) as compared to females (1 of every 28 females).
- Female sex is associated with increased risk of depression and anxiety in those with epilepsy.
- We lack large, population-based studies for antiseizure medications' effects on sexual function and fertility.
- There is no association between oral contraceptive use and seizure frequency.
- Registry-based data on antiseizure medication in pregnancy continue to support the recommendation that valproic acid should be avoided in women of reproductive age and favor treating women considering pregnancy with lamotrigine or levetiracetam.
- Few population-level data remain on women with epilepsy in pregnancy, during lactation, and during the menopausal transition.

Epidemiology of Epilepsy

Almost 50 million individuals worldwide are estimated to have active epilepsy at any given time [1, 2]. The prevalence of epilepsy is defined as the number of persons with epilepsy in a defined population at one point in time, divided by the number of persons in that population and time. The incidence of epilepsy is defined as the number of new cases of epilepsy over a specified time period [1, 3]. The reported incidence and prevalence of epilepsy vary widely across studies. Reasons for these estimate differences may include variation in the case ascertainment methods, diagnostic criteria, or study location, or because of concealment by some individuals due to the stigma associated with epilepsy.

The overall prevalence of epilepsy is estimated to be between 3 and 10 cases per 1,000 persons, excluding febrile convulsions, single seizures, and inactive epilepsy [3–8], but the median lifetime prevalence of epilepsy has been reported to be as high as 15.4 per 1,000 (4.8–49.6) in rural areas and 10.3 per 1,000 (2.8–37.7) in urban areas of low-income countries [5]. The prevalence of epilepsy is slightly higher in males than females in many door-to-door and record-review studies. However, any sex difference in prevalence is slight

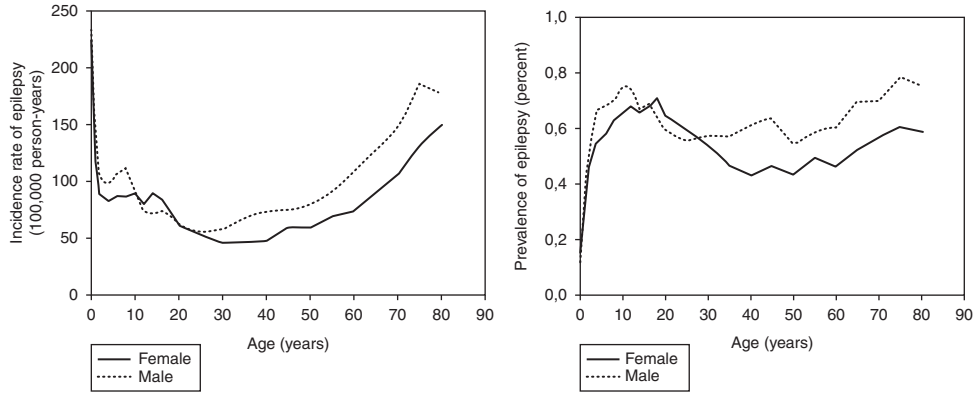

Figure 1.1 A. Left panel: Age- and gender-specific incidence of epilepsy in Denmark. Estimates were based on 5,491,652 people born in Denmark followed up for development of epilepsy between 1995 and 2002, including 33,140 who developed epilepsy. The incidence measures the number of new cases per 100,000 person-years at risk. B. Right panel: Five-year prevalence of epilepsy in Denmark. Estimates were based on 4,977,482 persons born in Denmark and resident in Denmark on December 31, 1999, including 28,303 diagnosed with epilepsy between 1995 and 1999. Modified with permission from Christensen et al. [4]

and usually not significant [1, 3, 9]. Some studies do continue to report a sex difference in epilepsy prevalence. For example, in a Danish study using population-based data from a national registry (Figure 1.1A), the prevalence of epilepsy was higher in men compared to women for most age groups, except for the 16–25 age group [4, 10]. In this study, men were also found to have higher incidence rates than women in all age categories, again with the exception of the 10–20 age group (Figure 1.1B) [4].

The overall incidence rate of epilepsy is usually reported to be about 40–70 cases per 100,000 person-years in high-income countries, and about 100–190 cases per 100,000 person-years in low-income countries [2, 3, 5, 9, 11]. In a recent systematic review and meta-analysis, the estimated incidence rate of epilepsy was reported to be 48.86 per 100,000 person-years for high-income countries and 138.99 per 100,000 person-years for low- and middle-income countries [3, 11]. The incidence of epilepsy is often reported to have a bimodal distribution (Figure 1.2). It is highest in early childhood, lowest in the early adult years, and then increases again after age 55 with the highest reported incidence in those older than 75 years of age [12]. A similar pattern is described in both males and females.

The lifetime risk of epilepsy is the probability that a person will develop epilepsy over their lifetime. Based on calculations in a population-based study, 1 in 26 people will develop epilepsy during their lifetime, and men have a higher risk of developing epilepsy (1 of every 21 males) than women (1 of every 28 females) [13]. There does not appear, however, to be a sex difference in the incidence of drug-resistant epilepsy [14].

The causes behind these potential sex differences have not been elucidated. One hypothesis of why epilepsy may be more common in men than in women is that men have a higher incidence of traumatic brain injury, which in turn is associated with epilepsy. Focal epilepsy has also been found to occur more frequently among men than women (Figure 1.3) [2, 3, 10, 12]. Notably, the higher incidence of epilepsy in men relative to women has not been reported in adolescents. This may be due to the higher incidence of idiopathic generalized epilepsy in women between the ages

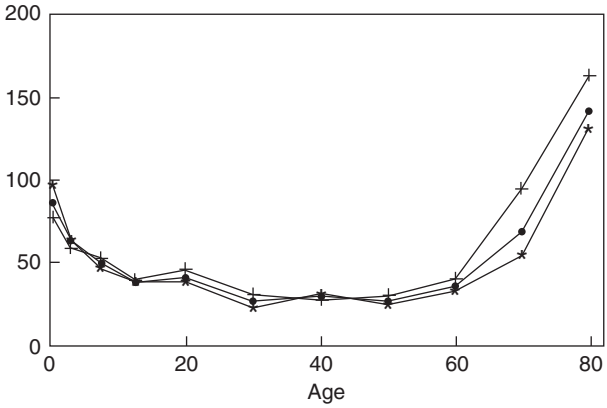

Figure 1.2 Age- and gender-specific incidence per 100,000 of epilepsy in Rochester, Minnesota, 1935–84. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

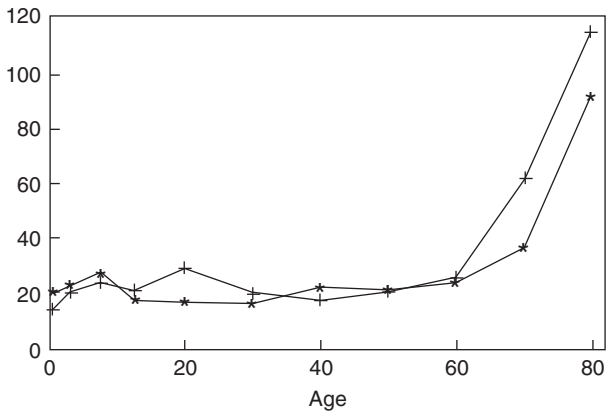

Figure 1.3 Age- and gender-specific incidence per 100,000 of focal epilepsy in Rochester, Minnesota, 1935–84. Male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

of 12 and 20 years (Figure 1.4). The reason for increased incidence of generalized epilepsy in women relative to men in adolescence is not fully known but may be attributed to genetic or hormonal factors [10]. If female sex hormones contribute to the development of idiopathic generalized epilepsy in women, this difference would be more obvious before menopause and decline with age, which is demonstrated in the Danish study just discussed [10, 15]. It has also been suggested that the higher reported estimates in males compared to females may be due to a sex bias in reporting due to the concealment of symptoms by women in cultures where women might be considered "unmarriageable" if they have epilepsy [1, 3].

Comorbidities

A number of mental health conditions are increased in persons with epilepsy as compared to those without epilepsy [16, 17]. Studies have shown that major depression, anxiety, and

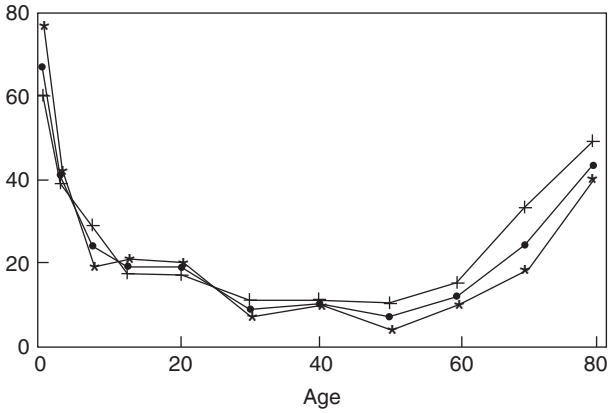

Figure 1.4 Age- and gender-specific incidence per 100,000 of generalized onset epilepsy in Rochester, Minnesota, 1935–84. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

psychosis are associated with an increased risk for developing epilepsy and vice versa [18, 19]. This bidirectional relationship suggests a possible shared pathogenetic origin [18]. Having epilepsy is also associated with a higher prevalence of somatic comorbidities as compared to the general population [8, 20, 21]. Here, we discuss sex differences in the epidemiology of mood and anxiety as well as sleep disorders in epilepsy.

Psychiatry

Mood Disorders in Epilepsy

Mood disorders are prevalent in those with epilepsy, with major depression the most common [22, 23]. Female sex is associated with depression in both those with and without epilepsy [22]. In those without epilepsy, the prevalence of depressive mood disorders has been reported to be approximately two times higher in women than in men. However, this sex difference is less pronounced in those with epilepsy [24–27].

In a nationally representative Canadian health survey using structured interviews for the assessment of major depressive disorder, depression was identified in 13% of those with epilepsy compared to 7% of those without epilepsy [22]. Women with epilepsy (WWE) had 2.6 times the odds (95% confidence interval [CI], 1.6–4.3) of depression as compared to men with epilepsy [22]. A meta-analysis found that the odds of active depression was higher in people with epilepsy compared to those without epilepsy (odds ratio [OR] 2.77; 95% CI, 2.09–3.67) [27, 28]. The lifetime prevalence of major depressive disorder in those with epilepsy was 17.4% (95% CI, 10.0–24.9), compared to 10.7% (95% CI, 10.2–11.2) in those without epilepsy, with an OR of 1.8 (95% CI, 1.0–3.1). Furthermore, the lifetime prevalence of major depressive disorders, while still increased for those with epilepsy, has been shown to decline with age in women while remaining relatively stable in men (Figure 1.5A) [16].

While there are fewer studies examining the incidence of postpartum depression (PPD) in WWE, smaller studies have reported an increased frequency of PPD in WWE compared to women without epilepsy (WWoE). Increased rates of depression in WWE have been confirmed in a Norwegian population-based study of mothers with a peripartum depression rate of 26.7% in WWE as compared to 18.9% in WWoE ($p < 0.001$) [29]. No specific

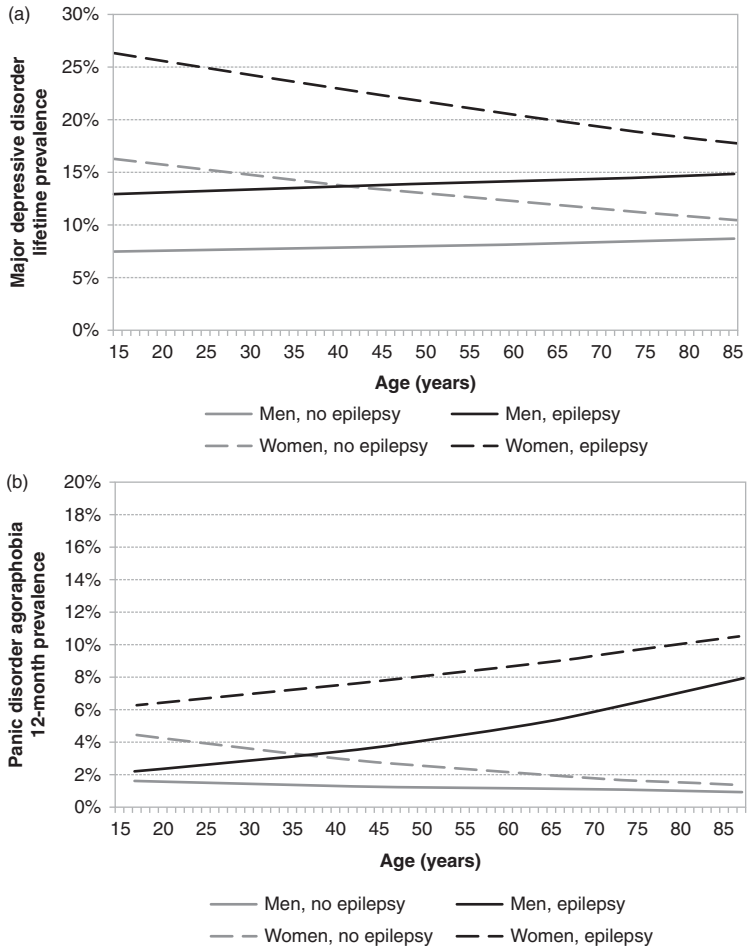

Figure 1.5 A. Logistic regression (fitted) models predicting the lifetime prevalence (proportion in percentage) of major depression disorder (on the y-axis) based on age (on the x-axis) and gender. Reproduced with permission from Tellez-Zenteno et al. [16]. B. Logistic regression (fitted) models predicting the 12-month prevalence (proportion in percentage) of panic disorder/agoraphobia (on the y-axis) based on age (on the x-axis) and gender. Reproduced with permission from Tellez-Zenteno et al. [16]

causative factor has been identified to explain this disparity although frequent seizures, polytherapy, previous psychiatric disease, and sexual or physical abuse are all associated with a higher risk of peripartum depression in WWE [30]. Similarly, a recent study of a nationally representative sample of admissions to US hospitals for childbirth showed increased rates of 30-day readmission for psychiatric illness among WWE (OR, 10.13; 95% CI, 5.48–18.72). The most common cause for psychiatric readmission in these women was mood disorder.

Anxiety Disorders

Anxiety is known to be a significant psychiatric comorbidity in epilepsy. A bidirectional association between anxiety and epilepsy has been described with an almost twofold increase in odds of developing anxiety in people with epilepsy as compared to those without [19].

In a cross-sectional, population-based study from the United Kingdom using diagnoses from primary care records, anxiety disorders were reported in 11% of 5,834 people who had epilepsy, compared to 5.6% of 831,163 who did not have epilepsy [31]. The risk of anxiety was higher in both men and women with epilepsy compared to control, but higher in WWE overall. For example, in the 16–64 year age group, anxiety was reported in 14.2% of 2,338 WWE compared to 7.5% of 410,851 WWoE (relative risk [RR], 1.95; 95% CI, 1.8–2.2). In the same age group, 9.4% of 2,321 men with epilepsy and 3.8% of 420,312 men without epilepsy (RR 2.6; 95% CI, 2.3–2.9) were found to have anxiety. In the 64 years and older age group, 9.0% of 642 WWE had anxiety compared to 7.8% of 118.516 WWoE (RR, 1.2; 95% CI, 0.9–1.5). In the same age group, anxiety occurred in 7.5% of 533 men with epilepsy, and only in 3.8% of 86,130 men without epilepsy (RR, 2.0; 95% CI, 1.5–2.7). Finally, in a population-based Canadian survey using structured interviews based on DSM-IV, both panic disorder and agoraphobia became more prevalent with age (and were found to be higher in women compared to men with epilepsy), but this was not found to occur in the general population (Figure 1.5B) [16]. A recent meta-analysis calculated a pooled prevalence of anxiety disorders at 20.2% (95% CI, 15.3–26.0%) [28] as compared to approximately 9.4% of people in the general population [32]. A similar meta-analysis in youth (<18) confirmed that youth with epilepsy had significantly higher anxiety symptoms than youth without epilepsy (moderator coefficient d = 0.57, 95% CI, 0.32–0.83, p < .0005) [26]. For a more detailed review, see Chapter 2.

Sleep

Sleep disturbances are reported more frequently in adults with than in adults without epilepsy. Obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS), and sleep maintenance insomnia (difficulty staying asleep) are more commonly found in those with epilepsy than in those without [33–37]. Sleep disorders in people with epilepsy have also been associated with ongoing seizures and worse quality of life [38]. However, population-based studies on sleep disturbances in patients with epilepsy are lacking. Furthermore, there has been little attention to sex differences in those existing smaller studies.

In a mail survey of 1,183 Dutch outpatients, the 6-month prevalence of sleep disturbances in people with focal epilepsy was more than two times greater than that of healthy controls (38.6% vs. 18.0%) [39]. This was not due to any one particular type of sleep disturbance; all sleep disturbances were significantly more prevalent in patients with epilepsy. A prospective Swiss study of 100 adult epilepsy patients found sleep symptoms were three times as likely (30% vs. 10%) in a population of people with epilepsy compared with controls [35]. In small case series, OSA has been reported in 10% of adults with epilepsy, 20% of children with epilepsy, and approaching 30% in patients with drug-resistant epilepsy [33]. Furthermore, OSA occurs more frequently in those who are older, male, overweight, and with drug-resistant or late-onset epilepsy [33, 34]. Identification and treatment of sleep disorders may be important: a retrospective review of epilepsy patients with OSA treated at the Cleveland

Clinic showed improvement in seizure frequency with treatment of OSA using positive airway pressure [40].

Notably, more sleep problems are encountered by children with epilepsy than their healthy siblings and other healthy controls [34, 37]. Sex, however, does not contribute to the frequency of problems with sleep in children [34]. For a more detailed review, see Chapter 3.

Epilepsy in Childhood and Adolescence

Inheritance and Genetics

Genetic testing, although primarily used in children, is climbing as increasing numbers of known mutations are identified. Several factors have been found to be associated with a predisposition to epilepsy, particularly in a family where one member is already affected. Affected children have a greater risk of being born to a mother with epilepsy (8.7%) as compared to a father with epilepsy (2.4%) [41]. How early a parent developed epilepsy also predicts the likelihood of a child developing epilepsy [41]. The children of parents who develop epilepsy before age 20 have a 2.3–6% risk of epilepsy in their offspring as compared to 1.0–3.6% in the offspring of those who develop epilepsy after age 20 [41]. Furthermore, when the parent also has epilepsy, the risk of epilepsy in offspring with epilepsy increases from approximately 3% to 8% [41].

The epilepsy syndrome or seizure type also contributes to the likelihood of epilepsy developing in relatives. Occurrence of epilepsy in relatives is increased when the proband has idiopathic epilepsy with seizures such as myoclonic or absence seizures. In those with myoclonic seizures, a 4–8% risk of any epilepsy in offspring is seen, while in those with absence seizures, a 5–9% risk of any epilepsy is observed (Figure 1.6) [41]. The risk of epilepsy in those related to individuals with generalized epilepsies is greater than in those related to individuals with focal epilepsy in some studies; however, this has not been observed in all studies (Figure 1.6) [41, 42]. The pattern of inheritance in generalized epilepsies is unknown and the development of epilepsy is suspected to be complex: an interaction between genetic susceptibility and the environment [43]. A recent meta-analysis

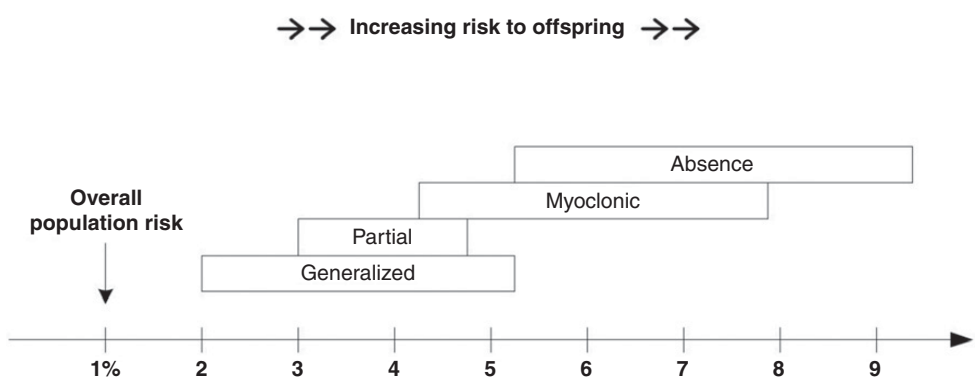

Figure 1.6 Percent of offspring affected with epilepsy. Reproduced with permission from Winawer and Shinnar [41]

of electroencephalograms (EEGs) of asymptomatic first-degree relatives of patients with juvenile myoclonic, childhood absence, and Rolandic epilepsies suggests that the susceptibility to seizures in some of these families may be compatible with Mendelian genetics [44]. For a more detailed review, see Chapter 6.

Sex Differences in Epilepsies in Children and Adolescents

Sex differences have been identified in various epilepsy syndromes. Idiopathic generalized epilepsy, which accounts for 15–20% of the epilepsies, can be found more frequently in females than in males [45]. Childhood absence epilepsy (CAE) was reported in 2.5% of boys compared to 11.4% of girls in a Norwegian population-based study [46]. Juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) were more common among females than males using data from 2,488 individuals with epilepsy from a Danish outpatient epilepsy clinic and the Danish Twin Registry [10]. Juvenile absence epilepsy was three times more common in females than males (76% vs. 24%), whereas JME was 1.5 times more common in females than males (61% vs. 39%) [10]. However, there has been less agreement as to whether sex differences exist in focal epilepsies. While one prospective study of 996 patients with suspected seizures conducted over a 4-year period in Australia reported an equal sex distribution of hippocampal sclerosis (81% in men vs. 79% in women) [47], another retrospective study of 153 patients presenting for presurgical evaluation in Germany found that the expression of focal epilepsy due to mesial temporal sclerosis is not the same in females and in males [48]. Females had higher odds of experiencing isolated auras than males (OR, 2.1; 95% CI, 1.1–4.2) and lower odds of having focal to bilateral tonic-clonic seizures (OR, 0.44; 95% CI, 0.21–0.92). Furthermore, they also found that electrographic findings were more likely to be on the same side of hippocampal sclerosis in females compared to males (98% vs. 84%). For a more detailed review, see Chapter 7.

Catamenial Epilepsy

Catamenial epilepsy is defined as a doubling in daily seizure frequency during specific phases of the menstrual cycle [49]. Three categories of catamenial seizure patterns have been described: perimenstrual, periovulatory, and entire luteal phase in anovulatory cycles [49]. Population-based studies exploring the prevalence of catamenial epilepsy are lacking. However, a catamenial pattern was found in 39% of women with localization-related epilepsy (LRE) in a prospective study of 87 women [50] and 31% of adolescent females in a prospective study of 42 WWE from an Egyptian pediatric neurology clinic [51]. The laterality and focality of epilepsy may play a role in the likelihood of cyclical hormonal fluctuations affecting the seizure pattern [52]. For a more detailed review, see Chapter 8.

Epilepsy in Women of Reproductive Potential

Fertility and Epilepsy

Sexual Dysfunction

There are no population-based studies examining sexual dysfunction in WWE. While sexual dysfunction has been documented in both men and women with epilepsy, very little

research has been done to investigate gender differences in the rates of dysfunction. However, sexual dysfunction has been found to be increased in epilepsy patients of both sexes. Persons with epilepsy have reported reduced quality of life and most commonly report symptoms of depression, decreased sexual desire, and problems with orgasms. Women with epilepsy also often report vaginal dryness [53].

Smaller series show that WWE are more likely to suffer from sexual dysfunction than WWoE. The particular neural networks involved in epilepsy may affect the occurrence of sexual dysfunction. A US study explored sexual dysfunction in 57 reproductive-aged women on antiseizure medication (ASM) monotherapy recruited from tertiary epilepsy centers as compared to 17 WWoE. Increased sexual dysfunction was found in women with generalized epilepsies (20.0%) or focal epilepsies (20.7%) as compared to controls (9%) [54].

Furthermore, sexual dysfunction is seen more frequently in right as compared to left temporal lobe epilepsy (TLE) in both men and women [55]. A controlled prospective study of 36 women with TLE recruited from a neurology outpatient clinic and 12 controls recruited from the community found that sexual function scores were substantially worse with right TLE as compared to left TLE. Additionally, women with right TLE (50%) and women with left TLE (30%) had increased rates of sexual dysfunction as compared to WWoE (8.3%). However, these differences were only significant for those with right TLE [55].

Antiseizure medications have been believed to play a role in sexual dysfunction in epilepsy. In particular, some older, enzyme-inducing ASMs may contribute to sexual dysfunction due to central nervous system changes or through changes in the levels of hormones supporting sexual behavior. Enzyme-inducing ASMs increase sex hormone-binding globulin and thereby decrease bioavailable testosterone, which may contribute to the emergence of sexual dysfunction [55]. While not statistically significant, 40.7% of WWE receiving an ASM reported increased sexual dysfunction compared to 33.3% of those not receiving an ASM in the same study [55]. However, recent studies have also found no association between sexual dysfunction and enzyme-inducing ASMs after controlling for sex [53].

Reproductive Dysfunction and Fertility

In WWE, menstrual cycle irregularities, increased risk of infertility, and/or signs of polycystic ovary syndrome (PCOS) are frequently encountered. Both seizures and ASMs have been causally implicated [56]. Two of the greatest challenges in comparing the results from studies looking at menstrual disorders in WWE are the lack of menstrual disorder definition and the limited number of population-based studies. Most published studies report data from highly selective, biased populations (e.g., women referred to a neuroendocrine clinic).

In a retrospective, questionnaire-based study of 265 WWE and 142 matched WWoE from three different Norwegian hospitals, menstrual disorders were significantly higher in WWE (48.0%) than in controls (30.7%) [57]. In other studies, menstrual disorders were more common in WWE: for example, 32% in one retrospective US analysis of 100 women with focal epilepsy [58]. In a controlled study, 12 of 36 (33.3%) of WWE compared to 14 of 100 (14%) community-based WWoE ($p = 0.02$) had a menstrual disorder [59].

Menstrual cycle irregularities, anovulation, higher androgen levels, carbohydrate intolerance with obesity, and polycystic-appearing ovaries are all characteristics of PCOS. A lack of a standardized definition of PCOS may explain the varying reported rates in women both with and without epilepsy, although again, there is a lack of population-based

studies of PCOS in WWE [60]. In a Finnish study examining reproductive endocrine function in 148 WWE, PCOS was found to occur in 28% of WWE, 52% of WWE on valproate (VPA), and 11% of controls. Women with epilepsy on VPA were significantly more likely to have PCOS when compared to controls (OR, 5.46; 95% CI, 2.23–13.03) [61]. A meta-analysis including 556 WWE treated with VPA, 593 women treated with other ASMs, 120 untreated WWE, and 329 healthy controls, found the odds of developing PCOS was 1.94 times greater (95% CI, 1.28–2.95) in VPA-treated WWE compared to other ASM-treated women [60]. The possibility of developing features of PCOS in those treated with VPA seems to be age-dependent [62]. In a prospective US study of 225 WWE taking VPA compared to 222 WWE taking lamotrigine (LTG), the occurrence of PCOS symptoms occurred more frequently in women started on VPA rather than LTG before the age of 26 years compared to WWE in whom VPA was started at the age of 26 years or older [62].

Valproate continues to show similar results in more recent studies. A US retrospective study investigated the risks of infertility and impaired fecundity of 1,000 WWE via the Epilepsy Birth Control Registry (EBCR) [63]. Of the 373 WWE, 724 pregnancies occurred with 445 births. While the rate of live births was similar among WWE on no ASM (71.3%), ASM monotherapy (71.8%), and polytherapy (69.7%), glucuronidated ASM (LTG) had the highest ratio of live birth/pregnancy compared to enzyme-inhibiting ASM (VPA), which had the lowest (89.1% vs. 63.3%; RR, 1.41; 95% CI, 1.05–1.88).

Another notable pattern of reproductive dysfunction described in patients with epilepsy is hypothalamic amenorrhea – a severe yet common pattern of hypogonadotropic hypogonadism. In one study, 50 women with TLE referred for neurologic evaluation were studied, with eight (16%) found to have amenorrhea. This is much higher than the expected frequency of 1.5% in the general population [64]. Furthermore, amenorrhea has been found to occur more commonly in women with right TLE than women with left TLE [59, 65]. Unfortunately, we do not believe that population-based estimates of amenorrhea in WWE have been published.

Overall fertility has also been examined in WWE. There are population-based data examining fertility rates in WWE from 1991 to 1995 compared to the 1993 fertility rates for England and Wales [66]. The fertility rate in WWE aged 15–44 was 47.1 live births per 1,000 women per year (95% CI, 42.3–52.2), compared with a national rate of 62.6. The most significant decrease in fertility rates was among WWE in the 25–39 year age groups ($p < 0.001$). Reassuringly, a US study of women with and without epilepsy seeking pregnancy found no differences in pregnancy rates or time to pregnancy [67]. This may suggest that the lower birth rates seen in WWE may be less due to reproductive dysfunction as compared to lower marriage rates, fear of birth defects, and/or concern for an increased risk of epilepsy in the offspring [68]. In a population-based study of 19 US states, 55.5% (95% CI, 51.3–59.7) of those with epilepsy were married or in a common-law relationship compared to 64.1% (95% CI, 63.6–64.7) of those without epilepsy. Of those with epilepsy, 22.9% (95% CI, 20.0–26.2) were formerly married compared to 18.0% (95% CI, 17.6–18.3) of those without epilepsy. Finally, 21.5% (95% CI, 17.7–26.0) of those with epilepsy were never married compared to 17.9% (95% CI, 17.4–18.4) of those without epilepsy [8]. Similar findings were reported in an Indian study of 300 epilepsy patients. Among those with epilepsy, 55.5% of men and 44.6% of women were never married compared to 43.3% of men and 22.3% of women in the general population (n = 4,687). Indeed, only 44.5% of men and 51.1% of women with epilepsy were currently married compared to 56.2% of men and 75.7%

of women in the general population. No men with epilepsy and 4.3% of WWE were divorced compared to 0.5% of men and 2% of women in the general population [69].

As in the general population, pregnancies in WWE are often unplanned. In the EBCR study, 78.9% of WWE reported having at least one unintended pregnancy with 65.0% of all 804 pregnancies being unintended. This is significantly greater than the 45–51% range of the general US population of childbearing women having unintended pregnancies [70]. However, according to a survey administered by the Centers for Disease Control and Prevention that randomly sampled 73,619 postpartum women from 13 US states and adjusted for covariates including age, race, ethnicity, and socioeconomic status (SES), the 541 (0.7%) WWE did not have a higher rate of unintended pregnancy when compared to WWoE [71].

More population-based studies about reproductive dysfunction in WWE are needed. For a more detailed review, see Chapter 9.

Hormonal Contraceptives and Epilepsy

As just described, pregnancies are often unplanned. Contraceptive management in WWE is paramount due to the possible maternal and fetal complications if contraception fails. Furthermore, the use of enzyme-inducing ASMs can result in the failure of common oral contraceptives (OCs) and may contribute to the relatively high number of unplanned pregnancies in WWE [72, 73]. Prepregnancy counseling for all WWE of childbearing age is necessary.

The prevalence of contraceptive use in 1,630 Dutch women of childbearing age on ASMs was calculated in a study using a population-based pharmaceutical dispensing database [74]. The authors found that only 34.3% of ASM users were prescribed highly effective contraceptives as compared with 41.2% of the general population of women of childbearing age ($p < 0.001$). They also found that of WWE who used enzyme-inducing ASMs in combination with a highly effective contraceptive method, 43.5% were on an OC containing less than the recommended 50 μg of estrogen. These findings are consistent with a large, population-based study of childbearing WWE on ASMs in the United Kingdom. This latter study found that 16.7% of WWE were on OC, and of those on both an enzyme-inducing ASM and an OC, 56% were on OC with an estrogen content less than 50 μg [75].

Importantly, despite the well-known effects of estrogen on lowering seizure threshold, an association between estrogen-containing OC and seizure exacerbation in WWE has not been seen. A large UK cohort study of 17,032 WWE followed for up to 26 years examined whether there was a relationship between OC use and an increase in the incidence of epilepsy or seizures [76]. No association was found between OC use and the development of epilepsy in WWoE or between OC use and seizure frequency in WWE.

Preconception Counseling

There are no studies examining how commonly preconception counseling occurs in WWE. However, the evidence for the use of preconceptual folic acid by WWE was reviewed by a committee assembled by the American Academy of Neurology (AAN) and American Epilepsy Society (AES), and is discussed later in this section [77]. A prospective study of 970 pregnancies and 979 offspring in WWE reported a significant correlation between serum folic acid concentrations less than 4.4 nmol/L and malformations in newborns (adjusted OR, 5.8; 95% CI, 1.3–27) [78]. However, several other studies reviewed did not show

a relationship between folic acid and major congenital malformations (MCMs) but were insufficiently powered to exclude a significant risk reduction from folic acid supplementation.

The effectiveness of preconceptual folic acid supplementation was prospectively examined in an observational study by looking at the rate of MCMs in a group of women on ASM monotherapy in the United Kingdom [79]. In the 1,935 cases that received preconceptual folic acid, 76 MCMs (3.9%; 95% CI, 3.1–4.9) and eight neural tube defects (NTDs) (0.4%; 95% CI, 0.2–0.8) were observed. There were 53 occurrences of an MCM (2.2%; 95% CI, 1.7–2.9) and eight NTDs (0.34%; 95% CI, 0.2–0.7) in the 2,375 women who obtained folic acid but did not start taking it until later in the pregnancy (n = 1,825) or not at all (n = 550). Folic acid supplementation in this population of WWE was not associated with a reduction in the frequency of MCMs or NTDs. This study suggests that extrapolating findings from population-based studies of all pregnant women who took folate to groups of selected WWE enrolled in registries may be inappropriate. The higher risk of MCMs in WWE may be multifactorial and may also be explained by mechanisms other than those related to folic acid metabolism.

The prophylactic effect of folic acid supplementation on the likelihood of spontaneous abortion and preterm delivery was examined prospectively in pregnant WWE on ASMs. These WWE were all registered in the International Registry of ASM and Pregnancy (EURAP) at a single center, with 388 pregnancies in 244 patients investigated [80]. Women with epilepsy who did not supplement with folic acid were more likely to have a spontaneous abortion than those who did supplement (OR, 2.6; 95% CI, 1.2–5.6). Consequently, pregnancies with folic acid supplementation were associated with a significant reduction of spontaneous abortion.

As epilepsy is more prevalent among those with decreased SES, which is itself associated with unintended pregnancy [7, 71], it is important to examine whether WWE of childbearing age are being counseled appropriately preconceptually about folate and ASM selection, including the risks of fetal malformations. In a 2013 prospective study of 1,526 pregnancies in Scottish WWE, significantly different rates of preconceptual folic acid supplementation existed when the highest and lowest socioeconomic quintiles were compared (56.8% vs. 14.0%; RR, 4.1; 95% CI, 3.1–5.2), yet no associated difference in the rate of major malformations was found (4.4% compared to 4.7%, p = 0.84) [81].

The evidence regarding the effectiveness of preconception counseling for WWE, calculated by a decrease in adverse pregnancy outcomes, was published in a Cochrane review [82]. No studies met all study eligibility criteria. There is thus no strong evidence regarding the effectiveness of preconception counseling to decrease adverse pregnancy outcomes for WWE and their offspring [83]. More population-based studies are required. For a more detailed review, see Chapter 10.

Antiseizure Medications and Fetal Effects

The occurrence of fetal malformations is associated with the use of ASMs in pregnancy. Different ASMs are associated with different types of malformations in the offspring. Data on fetal effects of ASMs generally come from epilepsy and pregnancy registries, as randomized clinical trials are not possible in pregnancy. Registries are found in many countries and differ in methodology and outcomes. Pharmaceutical companies may collect pregnancy data related to their product while other registries are driven by independent research

groups who may collect and publish data on more than one ASM for comparison [84]. Here, we primarily discuss population-based studies reporting on ASM and the risk of MCMs.

A Finnish retrospective, population-based study of WWE using data from the National Medical Birth Registry showed a higher risk of MCMs in the newborns of WWE exposed to any ASM in utero (OR, 1.7; 95% CI, 1.1, 2.8) compared to the newborns of WWE not exposed to ASM. The odds of MCMs in infants exposed to in utero VPA monotherapy (OR, 4.2; 95% CI, 2.3–7.6) or polytherapy (OR, 3.5; 95% CI, 1.4–8.1) were also increased [85].

A systematic review and meta-analysis of international published registries examined the incidence of congenital malformations and other pregnancy outcomes after in utero ASM exposure [86]. Fifty-nine studies involving 65,533 pregnancies in WWE and 1,817,024 pregnancies in WWoE were included. The incidence of congenital malformations in offspring born to WWE was greater (7.1%; 95% CI, 5.6–8.5) compared to offspring born to WWoE (2.3%; 95% CI, 1.5, 3.1). The incidence was greatest for ASM polytherapy [16.8%; 95% CI, 0.5–33.1). The highest CM incidence rate belonged to VPA, at 10.7% (95% CI, 8.2–13.3) for monotherapy. Valproate monotherapy and polytherapy drugs that included phenobarbital (PB), phenytoin (PHT), or VPA significantly increased the risk of CM in offspring exposed in utero.

Data on newer-generation ASMs are emerging. A population-based cohort study of 837,795 infants born in Denmark investigated the relationship between in utero exposure to newer-generation ASMs during the first trimester of pregnancy and the likelihood of developing MCMs [87]. Of the 1,532 infants exposed to LTG, oxcarbazepine (OXC), topiramate (TPM), gabapentin (GBP), or levetiracetam (LEV) during the first trimester, 3.2% were diagnosed with an MCM compared with 2.4% who were not exposed to an ASM with an adjusted OR of 1.0 (95% CI, 0.7–1.4). Of 1,019 ASM-exposed newborns, an MCM was discovered in 38 (3.7%) exposed to LTG during the first trimester (OR, 1.2; 95% CI, 0.8–1.7), in 11 of 393 (2.8%) exposed to OXC (OR, 0.9; 95% CI, 0.5–1.6), and in 5 of 108 (4.6%) exposed to TPM (OR, 1.4; 95% CI, 0.6–3.6). Only 1 (1.7%) infant exposed to GBP (n = 59) and no infants exposed to LEV (n = 58) were diagnosed with MCMs, but the use of these ASMs is still less common in pregnancy.

A prospective, non-population-based, cohort study using data from the North American AED Pregnancy Registry (NAAPR) investigated 7,370 pregnancies among women taking ASM in the United States and Canada between 1997 and 2011. Pregnant women (n = 1,562) exposed to LTG were the main comparison group [88, 89]. The risk of major malformations was as follows: 9.3% (95% CI, 6.4–13.0%) for VPA; 5.5% (95% CI, 2.8–9.7%) for PB; 4.2% (95% CI, 2.4–6.8%) for TPM; 3.0% (95% CI, 2.1–4.2%) for carbamazepine (CBZ); 2.9% (95% CI, 1.5–5.0%) for PHT; 2.4% (95% CI, 1.2–4.3%) for LEV; 2.2% (95% CI, 0.6–5.5%) for OXC; 0.7% (0.02–3.8) for GBP; and 3.1% (0.4–10.8%) for clonazepam (CZP). In comparison, the risk of malformations in the infants exposed to LTG was 2.0% (95% CI, 1.4–2.8%) and 1.1% (95% CI, 0.4–2.6%) in the unexposed hospital population. The ASMs with significantly elevated unadjusted RRs when compared to LTG exposure included VPA (RR, 5.1; 95% CI, 3.0–8.5), phenobarbital (RR, 2.9; 95% CI, 1.4–5.8), and TPM (RR, 2.2; 95% CI, 1.2–4.0). Notably, prevalence of oral clefts was 1.4% (95% CI, 0.51–3.1%) in the TPM-exposed pregnancies, which was higher than in the study comparison group [88] or other reference populations [87, 90].

In 2014, the Australian Pregnancy Register published a prospective, cohort study of 1,572 pregnancies of both treated and untreated WWE aimed at determining the rate of major malformations after exposure to three newer ASMs (LTG, LEV, and TPM) [91].

Malformations were seen in 3.3% of infants of 153 untreated WWE. The proportion and risk of major malformations for those exposed to monotherapy were as follows: LTG, 4.6% (RR, 1.40; 95% CI, 0.51–3.80); TPM, 2.4% (RR, 0.73; 95% CI, 0.09–6.07); and LEV, 2.4% (RR, 0.75; 95% CI, 0.15–3.76). For those exposed to polytherapy ASM treatment, the proportion of major malformations were as follows: LTG, 5.5% (RR, 1.67; 95% CI, 0.61–4.59); TPM, 14.1% (RR, 4.32; 95% CI, 1.57–11.05); and LEV, 8.7% (RR, 2.25; 95% CI, 0.76–6.69).

Other adverse pregnancy outcomes reported in the offspring of ASM-treated WWE include small-for-gestational age (SGA) infants, decreased head circumference, and microcephaly, but many of these studies involved older-generation drugs with limited information on the contribution of newer-generation ASMs [92–95].

In a 2014 cohort study from the Medical Birth Registry of Norway, the risks of fetal growth restriction in 2,600 infants exposed in utero to newer or older ASM were investigated [96]. Comparisons were made to 771,412 unexposed infants of WWoE. The overall risk of SGA outcomes was significantly increased in infants exposed to an ASM (10.7%; OR, 1.17; 95% CI, 1.03–1.33), especially for TPM exposure (25.0%; OR 3.29; 95% CI, 1.70–6.39) compared to unexposed infants (8.9%). The overall risk of head circumference less than the 10th percentile was increased in infants prenatally exposed to an ASM (10.8%; OR, 1.24; 95% CI, 1.09–1.40) compared to unexposed infants (8.7%). The overall risk of decreased head circumference (less than 2.5th percentile) was increased in infants exposed in utero to ASM (3.4%; OR, 1.39; 95% CI, 1.12–1.72) and significantly increased for those exposed to TPM (14.9%; OR 7.21; 95% CI, 3.23–16.1) compared to unexposed infants (2.4%). An increased rate of SGA outcomes (10.3%; adjusted OR 1.15; 95% CI, 1.03–1.27) was found in the 3,773 infants born to untreated WWE compared to unexposed infants of WWoE (8.9%). However, when comparing the rate of head circumference less than the 10th percentile to the reference group of unexposed infants, no difference was found.

There have also been studies examining the association between ASM use and cognitive outcomes in children. A prospective, observational (non-population-based) study from the NAAPR examined the cognitive effects of fetal exposure to ASM in 309 children at 3 years of age [97]. A nonexposed control group was not included. Pregnant WWE were enrolled who were taking ASM monotherapy (CBZ, LTG, PHT, or VPA). Lower intelligence quotient (IQ) scores were found in 3-year-old children who had been exposed in utero to VPA compared to children exposed to any other ASM. A dose-dependent relationship between VPA use and IQ was noted. These findings persisted to 4.5 years of age [98]. The mean IQ after adjustment at age 4.5 years was 106 (95% CI, 102–109) for those exposed in utero to CBZ, 106 (95% CI, 102–109) for LTG, 105 (95% CI, 102–109) for PHT, and 96 (95% CI, 91–100) for VPA. Frequency of marked intellectual impairment decreased with age in children exposed to LTG, PHT, and CBZ, but not for children whose mothers took VPA. Verbal abilities were found to be impaired compared to nonverbal skills in all four groups studied. As expected, maternal IQ correlated with children's IQ, except for those children with in utero exposure to VPA where the authors found IQs to be significantly lower. Right-handedness was seen less frequently in children exposed to ASM overall when compared to a normative sample of 187 unexposed children (86% vs. 93%; $p = 0.0404$), especially in the VPA (79%, $p = 0.0089$) and LTG groups (83%; $p = 0.0287$). In addition, the exposed children in this study had relatively decreased verbal abilities compared to nonverbal abilities for children whose mothers had taken LTG ($p = 0.028$) or VPA ($p = 0.0063$) during pregnancy.

In utero VPA exposure was again associated with several reduced cognitive abilities (e.g., IQ, verbal, nonverbal, memory, and executive function) at 6 years of age.

Recent studies have also demonstrated a link between maternal use of VPA and an elevated risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in the offspring. A 2020 Swedish study of 14,614 children born between 1996 and 2011 and maternal use of VPA, LTG, and CBZ in WWE found that only VPA was associated with either ASD and ADHD ICD-10 outcomes [99]. In addition, a 2019 Danish population-based study of 913,302 singletons exposed to ASM in utero demonstrated a 48% increased risk of ADHD (adjusted hazard ratio, 1.48; 95% CI, 1.09–2.00) in children exposed compared to those unexposed to valproic acid [100].

An observational (non-population-based) study of WWE and their children was conducted through the Australian Pregnancy Register for WWE and Allied Disorders [101]. Researchers investigated the language skills of 102 school-aged kids exposed prenatally to ASM. Children exposed to VPA monotherapy or polytherapy were significantly more likely to have below normal language scores compared to children exposed to CBZ or LTG monotherapy, or polytherapy without VPA. For a more detailed review, see Chapter 11.

Seizure Control during Pregnancy

No population-based studies, to our knowledge, have examined seizure control during pregnancy. However, some of the pregnancy registries have studied this in selected WWE. The International Registry of ASM and Pregnancy reported prospectively documented seizure control and treatment in 1,956 pregnancies of 1,882 WWE [102]. Of all pregnant WWE, 58.3% were seizure free throughout pregnancy. Focal epilepsy (OR, 2.5; 95% CI, 1.7–3.9), polytherapy (OR, 9.0; 95% CI, 5.6–14.8), and OXC monotherapy (for tonic-clonic seizures only) (OR, 5.4; 95% CI, 1.6–17.1) predicted the occurrence of seizures. Seizure control stayed constant during pregnancy in 63.6% of WWE pregnancies. Of those, 92.7% remained seizure free during the complete pregnancy. In pregnant WWE, 17.3% had an increase in the frequency of seizures while 15.9% of pregnant WWE had a decrease. The same ASM treatment continued in 62.7% of the pregnancies.

The risk of seizing during pregnancy has been reported to be significantly decreased if there has been no seizures for a year before pregnancy, according to an Australian registry-based study of 841 ASM-treated pregnancies [103]. Of all ASM-treated WWE, 49.7% had seizures while pregnant. The risk of having seizures during pregnancy was 24.9%, with a minimum of 1 year of freedom from seizures before pregnancy, 22.8% with a minimum of 2 years of freedom from seizures, 20.5% with a minimum of 3 years of freedom from seizures, and 20% with 4 or more years of freedom from seizures. The association between the length of time of freedom from seizures prior to becoming pregnant and the chances of being seizure free during and after pregnancy was the most relevant finding of this study. With 1 year of freedom from seizures before pregnancy, the likelihood of seizures in pregnancy was decreased by 50–70% [103]. For a more detailed review, see Chapter 12.

Pregnancy and Epilepsy

Women with epilepsy have been found to have a higher risk of pregnancy and delivery complications. However, it is not clear if this is due to epilepsy or the use of ASMs during

pregnancy. A population-based study examined whether pregnant WWE had a greater likelihood of complications during pregnancy and also explored the effects of ASM use via databases on all births in Norway from 1999 to 2005 [104]. The outcomes included preeclampsia, gestational hypertension, eclampsia, vaginal bleeding, and prematurity. Women with epilepsy had greater odds of mild preeclampsia (OR, 1.3; 95% CI, 1.1–1.5) and delivery before week 34 (OR, 1.2; 95% CI, 1.0–1.5). Women with epilepsy on ASMs had higher odds of mild preeclampsia (OR, 1.8; 95% CI, 1.3–2.4), gestational hypertension (OR, 1.5; 95% CI, 1.0–2.2), vaginal bleeding late in pregnancy (OR, 1.9; 95% CI 1.1–3.2), and delivery before 34 weeks of gestation (OR, 1.5; 95% CI, 1.1–2.0) when compared to WWoE. However, these increased risks of complications were not seen in WWE not using ASMs.

A population-based study using the same databases, including all births in Norway, looked at whether WWE have greater odds of complications during labor and investigated the impact of ASMs [105]. Outcomes included induction, caesarean section, use of forceps and vacuum, abnormal presentation, placental abruption, mechanical disproportion, postpartum hemorrhage, atony, and decreased Apgar scores after 5 minutes. Elevated odds of induction (OR, 1.3; 95% CI, 1.1–1.4), caesarean section (OR, 1.4; 95% CI, 1.3–1.6) and postpartum hemorrhage (OR, 1.2; 95% CI, 1.1–1.4) were seen in WWE (on or off ASMs) compared with WWoE. However, even higher estimates were obtained in WWE on ASMs with ORs (95% CIs) of 1.6 (1.4–1.9), 1.6 (1.4–1.9), and 1.5 (1.3–1.9), respectively. The odds of an Apgar score less than 7 was higher in WWE on ASM (OR, 1.6; 95% CI, 1.1–2.4) compared to WWoE. Only a mildly increased likelihood of caesarean delivery was found among WWE without ASMs compared to WWoE (OR, 1.3; 95% CI, 1.2–1.5).

A retrospective study from 2011 examined complications during pregnancy and delivery in 205 WWE and compared them to a control group of WWoE matched for age and parity [106]. After adjustment for age, parity, education, smoking, medical conditions and body mass index, WWE treated with ASMs had increased odds of severe preeclampsia (adjusted odds ratio [AOR], 5.0; 95% CI, 1.3–19.9), bleeding in early pregnancy (AOR, 6.4; 95% CI, 2.7–15.2); induction (AOR, 2.3; 955 CI, 1.2–4.3); and caesarean section (AOR, 2.5; 95% CI, 1.4–4.7) when compared to WWoE. While WWE using ASMs had greater odds for pregnancy and delivery complications, WWoE not using ASMs had few complications. Increased risks of pregnancy complications were not observed among WWE with no ASM use as compared to WWoE. However, not all studies found an increased risk for pregnancy and perinatal complications among WWE using ASMs. In a Swedish population-based cohort study of 1,429,652 singleton births, out of which 5,373 were born to 3,586 WWE [107], with the exception of an increased rate of labor induction (adjusted relative risk [ARR], 1.30; 95% CI, 1.10–1.55), the risks of pregnancy and perinatal complications among WWE using ASMs were not increased when compared to WWE not using ASMs [107]. For a more detailed review, see Chapter 13.

Postpartum Monitoring

Lactation

Few population-based studies of breastfeeding WWE have been conducted. Pregnant WWE taking a single ASM (CBZ, LTG, PHT, or VPA) were enrolled between 1999 and 2004 in an observational prospective study from epilepsy centers in the United States and the United Kingdom. The implications of breastfeeding during ASM therapy on cognitive outcomes in

3-year-old children were investigated [108]. Of the 199 children studied, 42% were breastfed. There were no differences in IQs for breastfed children compared to non-breastfed children for all ASMs combined and for each of the four individual ASM groups. The mean adjusted IQ score (95% CIs) across all ASM-exposed infants who were breastfed was 99 (96–103) while for non-breastfed it was 98 (95–101). This investigation does not show adverse effects of breastfeeding during ASM therapy on cognitive outcomes in children exposed in utero to four common ASMs.

A prospective cohort study from Norway of children born to 78,744 mothers provided detailed information on motor skills, social skills, language, and behavior at 6 months, 18 months, and 36 months of age [109]. The children of WWE using ASMs were compared to a reference group of children born to parents without epilepsy. In children of women using ASMs, continuous breastfeeding was associated with less impaired development at both 6 and 18 months when compared with those with no breastfeeding or breastfeeding for less than 6 months. However, adverse development was associated with prenatal ASM exposure at 36 months regardless of breastfeeding status during the first year. Compared to the reference population, continuous breastfeeding during the first year occurred less frequently among women using ASMs, particularly with LTG monotherapy and polytherapy. For a more detailed review, see Chapter 18.

Epilepsy in Menopause

Menopause, Hormone Replacement Therapy

Treatment of epilepsy may disrupt the effects of hormone replacement therapy (HRT) and conversely HRT may influence the occurrence of seizures. During the menopausal transition, catamenial seizures may increase in frequency due to hyperestrogenism and then decrease afterward. Sexual dysfunction may be exacerbated due to the lack of estrogen in menopause and epilepsy itself [110, 111]. Menopause tends to occur about 3 years earlier with a history of one or more seizures per month for much of the duration of epilepsy and lifetime use of multiple enzyme-inducing ASMs [112]. Premature ovarian failure (POF) in WWE has been noted in some studies, but no predisposing factors such as epilepsy duration, seizure severity, or use of enzyme-inducing ASMs have been identified [65, 113].

Menopause may also affect ASM metabolism. Hormone replacement therapy may lower LTG levels [114], and although the evidence is mixed, ASM clearance may also be affected by menopause [115, 116]. No population-based studies of menopause in WWE have, to our knowledge, been conducted.

Bone Health

Osteoporosis is associated with both menopause and the use of ASMs. The occurrence of menopause and the use of ASMs in WWE concurrently may combine to exacerbate this risk. Osteoporosis and fractures may increase in menopausal WWE because of hypoestrogenism in menopause and the use of cytochrome P450-inducing ASMs [110].

A Danish, population-based, case-control study investigated fracture risk associated with various ASMs (124,655 fracture cases and 373,962 controls) using the National Hospital Discharge Register and the National Pharmacological Database [117]. After adjustment, a significant association was found between CBZ (OR, 1.18; 95% CI, 1.10–1.26), OXC (OR, 1.14; 95% CI, 1.03–1.26), CZP (OR, 1.27; 95% CI, 1.15–1.41), PB (OR, 1.79;

95% CI, 1.64–1.95), and VPA (OR, 1.15; 95% CI, 1.05–1.26) and the likelihood of fracture. This association was not seen in ethosuximide (ETX), LTG, PHT, PR, tiagabine (TGB), TPM, or vigabatrin (VGB). Age and sex did not impact the risk of fracture [117].

A 2020 population-based study of epilepsy patients enrolled in Taiwan's National Health Insurance between 1998 and 2011 examined the risk of fracture and cost associated with fracture comparing enzyme-inducing ASMs to non-enzyme-inducing ASMs [118]. This study found 6,995 fractures (3,686 in the enzyme-inducing group). The non-enzyme-inducing ASMs were less likely to be associated with fracture (hazard ratio [HR] of 0.70, 95% CI, 0.50–0.97). In multivariate analysis, female sex was associated with risk of fracture (adjusted HR 1.80; 95% CI, 1.09–2.97).

Women with epilepsy of reproductive age are also at risk of experiencing bone loss while on ASMs, as shown in a prospective US study of WWE in taking ASM monotherapy (CBZ, LTG, PHT, or VPA) [119]. Of note, no control group of WWoE was included for comparison. In the PHT group, a significant decrease (2.6%) was found at the femoral neck over 1 year, unlike those treated with CBZ, LTG, and VPA who did not have evidence of bone turnover. For a more detailed review, see Chapter 19.

Summary

Epilepsy is one of the most common neurological conditions affecting women and men of all ages. Women with epilepsy encounter particular issues throughout their life span, and we have only begun to collect the population-level data that allow us to make counseling recommendations in this population. There unfortunately remain few population-level data on WWE during hormonal transitions, including in pregnancy, during lactation, and during the menopausal transition.

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