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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

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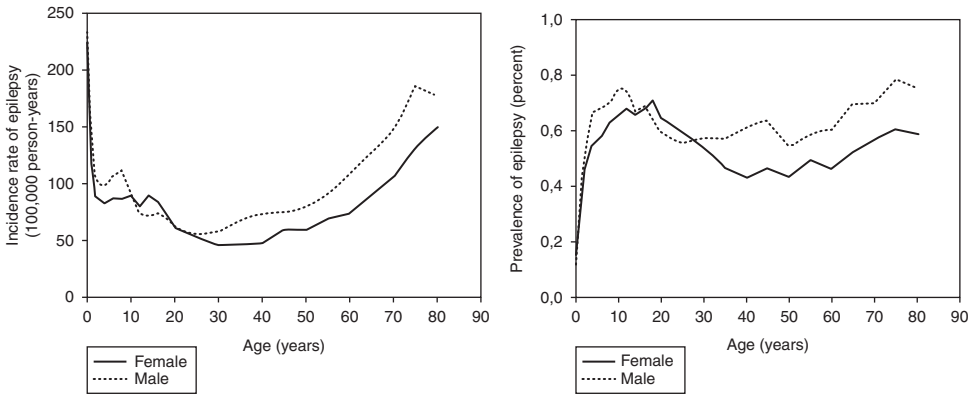

Figure 1.1 A. Left panel: Age- and gender-specific incidence of epilepsy in Denmark. Estimates were based on 5,491,652 people born in Denmark followed up for development of epilepsy between 1995 and 2002, including 33,140 who developed epilepsy. The incidence measures the number of new cases per 100,000 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

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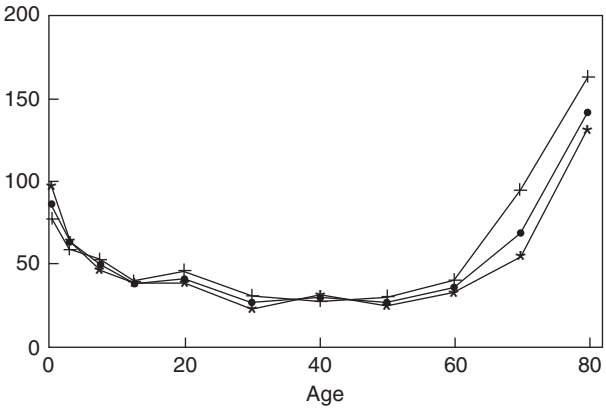

Figure 1.2 Age- and gender-specific incidence per 100,000 of epilepsy in Rochester, Minnesota, 1935–84. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

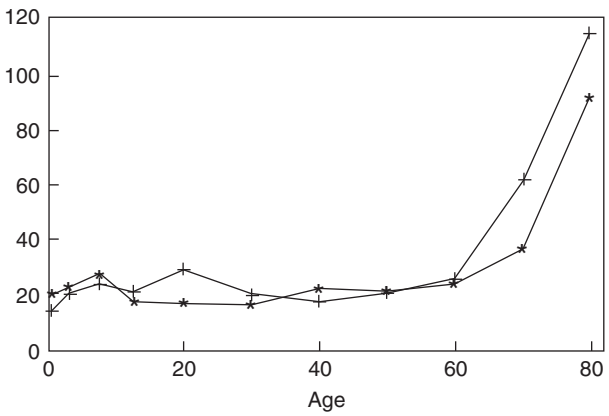

Figure 1.3 Age- and gender-specific incidence per 100,000 of focal epilepsy in Rochester, Minnesota, 1935–84. Male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

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

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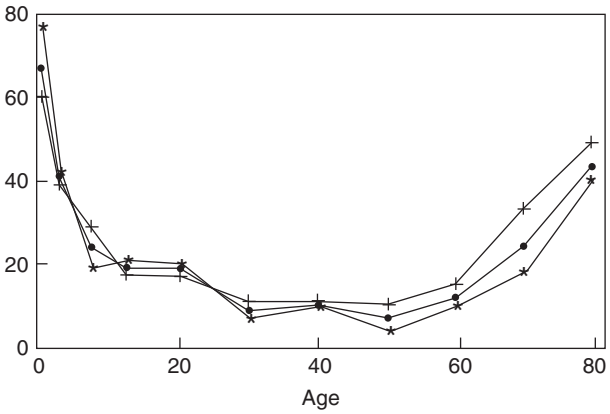

Figure 1.4 Age- and gender-specific incidence per 100,000 of generalized onset epilepsy in Rochester, Minnesota, 1935–84. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [12]

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

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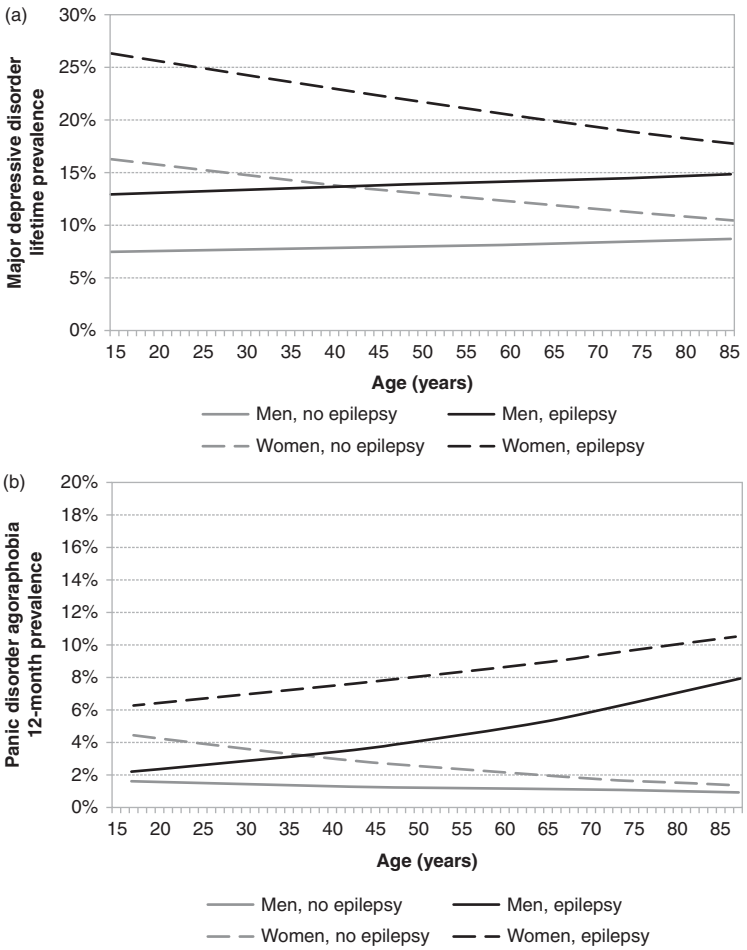

Figure 1.5 A. Logistic regression (fitted) models predicting the lifetime prevalence (proportion in percentage) of major depression disorder (on the y-axis) based on age (on the x-axis) and gender. Reproduced with permission from Tellez-Zenteno et al. [16]. B. Logistic regression (fitted) models predicting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

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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

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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

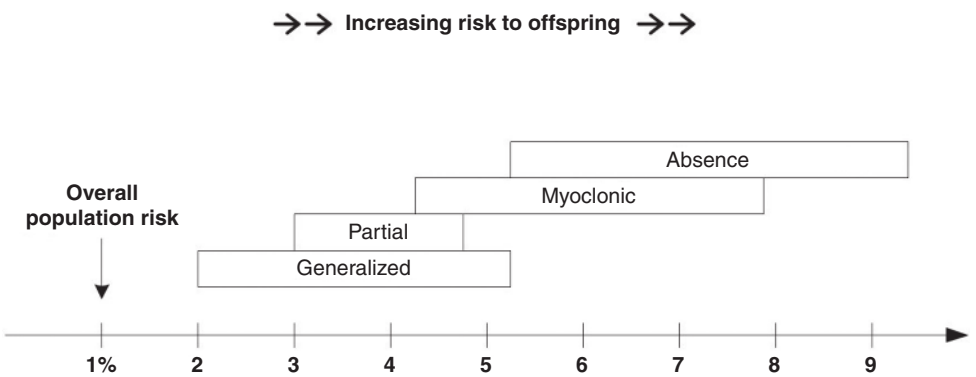

Figure 1.6 Percent of offspring affected with epilepsy. Reproduced with permission from Winawer and Shinnar [41]

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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

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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

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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%

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