Chapter 1

Epidemiology of women with epilepsy

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Key points:

- **Gender differences are observed in specific epilepsy syndromes**
- **Women with epilepsy (WWE) are at increased risk for depression, anxiety, sexual dysfunction, and infertility**
- **WWE of childbearing age encounter challenges associated with contraceptive therapy, pregnancy, and anticonvulsant use**
- **WWE during menopause face unique concerns related to hormone replacement therapy and osteoporosis**

Introduction

Epilepsy is one of the most common neurological conditions affecting men and women of all ages. In this chapter, we review the epidemiology of the epilepsies along with the epidemiology of comorbidity and special issues WWE encounter throughout their life.

Epidemiology of epilepsy

Fifty million individuals worldwide are estimated to have epilepsy at any given time [1]. Prevalence of epilepsy is defined as the number of persons with epilepsy in a specific population at one point in time, divided by the number of persons in that population and time. Incidence of epilepsy is defined as the number of new cases of epilepsy over a specified time period [1]. The reported incidence and prevalence of epilepsy varies widely between studies. Reasons for these estimated differences may include variations in the case ascertainment methods, the lack of accepted diagnostic criteria, the variations in the study location, and possible underreporting due to the stigma associated with epilepsy.

The overall prevalence of epilepsy is estimated to be between 5 and 10 cases per 1,000 persons, excluding febrile convulsions, single seizures, and inactive epilepsy [2–6], 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 developing countries [3]. The prevalence of epilepsy is slightly higher in males than females in many door-to-door studies and record-review studies. Still, the difference in prevalence between the genders is very slight and usually not significant [1, 7]. However, some studies do report a gender difference in the epilepsy prevalence. For example, in a Danish study

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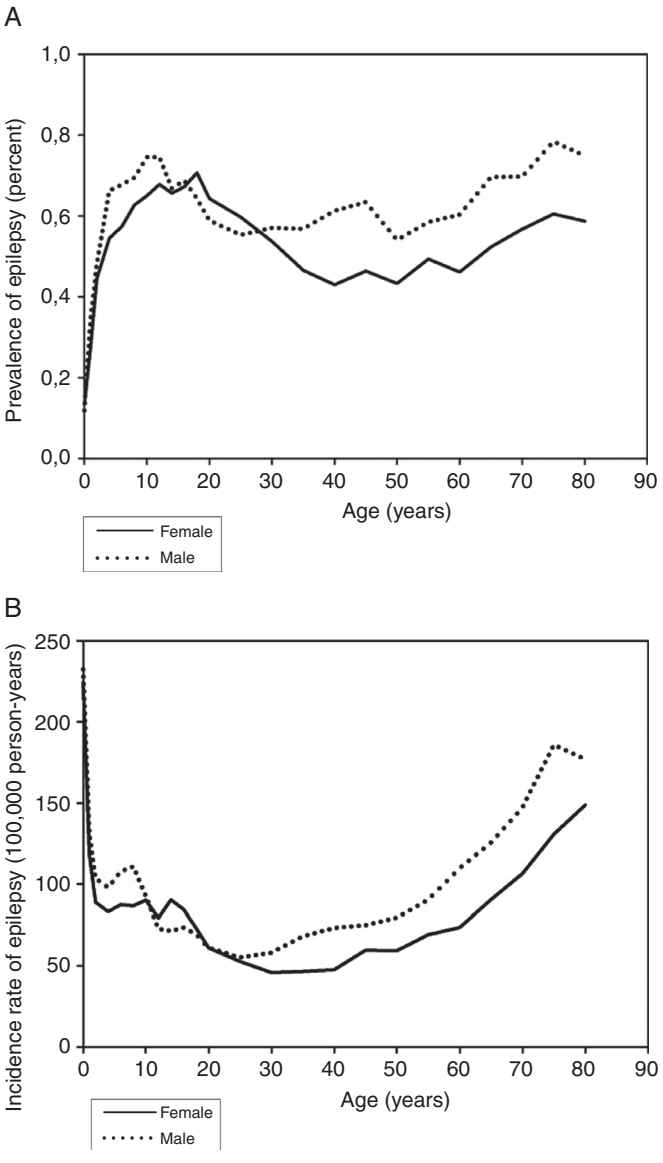

Figure 1.1: A: 5-year prevalence of epilepsy in Denmark. Estimates were based on 4,977,482 persons born in Denmark and resident in Denmark on December 31, 1999, including 28,303 diagnosed with epilepsy between 1995 and 1999. B: Age- and gender-specific incidence of epilepsy in Denmark. Estimates were 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. Reproduced with permission from Christensen et al. [2]

using population-based data from a national registry (Figure 1.1, A), the prevalence of epilepsy was higher in men compared to women for most age groups, except for the 16–25 year age group [2, 8]. In this study, men were also found to have higher incidence rates than women in all age categories with the exception of the 10–20 year age category (Figure 1.1, B) [2].

The overall incidence of epilepsy is usually reported to be about 40–70 cases per 100,000 person-years in developed countries, and about 100–190 cases per 100,000 person-years in developing countries [3, 7]. In a recent systematic review and meta-analysis, the median incidence of epilepsy was reported to be 45.0/100,000 person-years for high-income

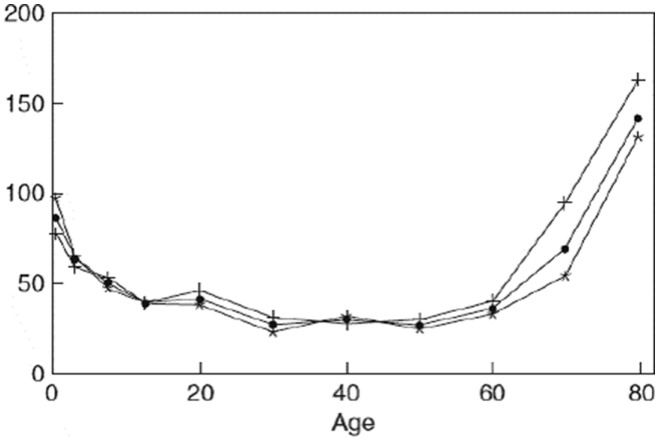

Figure 1.2: Age- and gender-specific incidence/100,000 of epilepsy in Rochester, Minnesota, 1935–1984. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

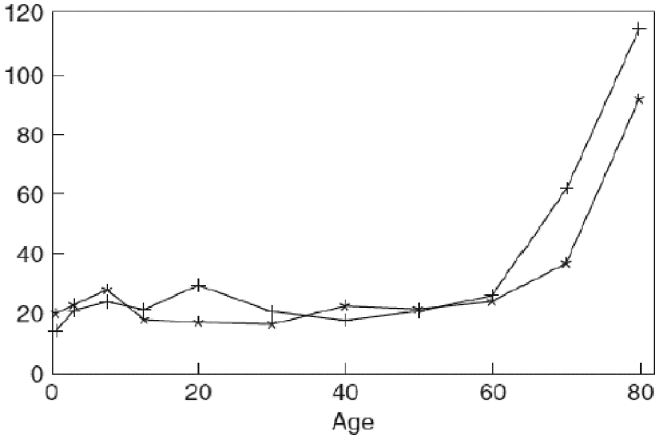

Figure 1.3: Age- and gender-specific incidence/100,000 of partial epilepsy in Rochester, Minnesota, 1935–1984. Male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

countries and 81.7/100,000 person-years for low- and middle-income countries [9]. The incidence of epilepsy is often reported to have a bimodal distribution (Figure 1.2). It is highest in early childhood, lowest in early adult years, and then increases again after age 55 with the highest reported incidence in those over 75 years of age [10]. A similar pattern is described in both males and females.

The lifetime risk is the probability that a person will develop epilepsy over his or her lifetime. Based on calculations in a recent 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) [11].

The causes behind these gender differences have not been elucidated. One hypothesis as to why epilepsy may be more common in men than in women is that men have a higher incidence of trauma-related disease, which in turn is associated with epilepsy. Focal epilepsy has also been found to occur more frequently among men than women (Figure 1.3). This higher incidence in men relative to women has not been reported in adolescents. This may be due to the higher incidence of primary generalized epilepsy (PGE) in

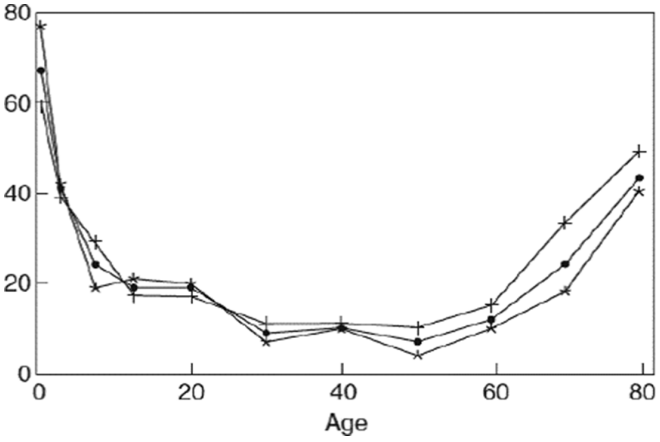

Figure 1.4: Age- and gender-specific incidence/100,000 of generalized onset epilepsy in Rochester, Minnesota, 1935–1984. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

women between the ages of 12 and 20 years (Figure 1.4). This increased incidence of generalized epilepsy in women relative to men in adolescence could be attributed to hormonal factors [8]. It has been hypothesized that sex hormones may contribute to the development of idiopathic generalized epilepsy in women, in which case this difference would be more obvious before menopause and decline with age, as demonstrated in the Danish study discussed above [8]. Furthermore, it has been suggested that higher reported estimates in males compared to females in many studies may be due to concealment of symptoms by women in certain cultures where women are considered "unmarriageable" if they have epilepsy [1].

Comorbidities

A number of mental health conditions are increased in persons with epilepsy compared to those without epilepsy [12]. Having epilepsy is also associated with a higher prevalence of somatic comorbidities compared to the general population [6, 13]. Here, we discuss gender differences in the epidemiology of mood and anxiety as well as sleep disorders in epilepsy. This is discussed in greater detail in Chapters 2 and 3.

Psychiatry

Mood disorders in epilepsy

Mood disorders are prevalent in those with epilepsy, with major depression being the most common mood disorder [14]. Recently, studies have shown that a history of major depression is associated with an increased risk for developing seizures and vice versa [15]. This two-way relationship suggests a possible shared pathogenetic origin [15].

Female gender is found to be associated with depression in those with or without epilepsy [14, 16]. Among women without epilepsy (WWoE), the prevalence of depressive mood disorders has been reported to be approximately two times higher in women than in men. 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 [14]. WWE were 2.6 times more

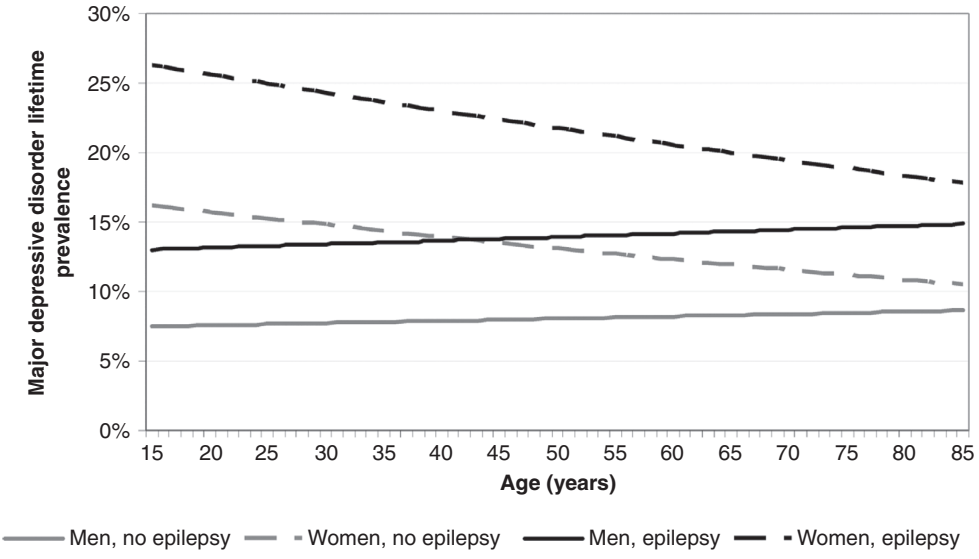

Figure 1.5: Logistic regression (fitted) models predicting the lifetime prevalence (proportion in percentage) of major depression disorder (on the y-axis) based on age (on the x-axis) and gender. Reproduced with permission from Tellez-Zenteno et al. [12].

likely (95% confidence intervals (CI), 1.6–4.3) to be depressed than men with epilepsy [14]. In another large Canadian population-based study using similar methodology, the odds of lifetime major depression was found to be higher in people with epilepsy compared to those without epilepsy [12]. 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 odds ratio (OR) of 1.8 (95% CI, 1.0–3.1). In other population-based studies lifetime prevalence has been estimated to be as high as 30% [80]. 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 1.5) [12].

While no population-based studies have examined the incidence of postpartum depression (PPD) in WWE, smaller studies have reported an increased frequency of PPD in WWE compared to WWoE. For example, an Italian study of 55 postpartum women with and without epilepsy found that PPD occurred in 39% of WWE compared to 12% of WWoE ($p<0.05$) [17]. No specific causative factor, however, has been identified to explain this disparity.

Anxiety disorders

Whereas much is known about the association between epilepsy and depression, less is known about the epidemiology of anxiety disorders in those with epilepsy.

In a cross-sectional, population-based study from the UK using diagnoses from primary care records, anxiety disorders were reported in 11% of people with epilepsy ($n = 5{,}834$), compared to 5.6% of those without epilepsy ($n = 831{,}163$) [18]. The risk of anxiety was higher in both men and WWE compared to control, but higher in WWE overall. In the female 16–64 year age group, anxiety was reported in 14.2% of 2,338 WWE

compared to 7.5% of 410,851 WWoE (RR, 1.95; 95% CI, 1.8–2.2). In the 64 year 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 a population-based Canadian health survey using structured interviews based on DSM-IV, those with epilepsy were more likely than those without epilepsy to report lifetime anxiety disorders with an OR of 2.4 (95% CI, 1.5–3.8). Of those with epilepsy, 12.8% (95% CI, 6.0–19.7) reported an anxiety disorder in the past 12 months compared to 4.6% (95% CI, 4.3–4.9) in the group without epilepsy. Similarly, 22.8% (95% CI, 14.8– 30.9) of those with epilepsy compared to 11.2% (95% CI, 10.8–11.7) of those without epilepsy reported a lifetime anxiety disorder. In both women and men with epilepsy, panic disorder and agoraphobia became more prevalent with age (and was found to be higher in women compared to men with epilepsy) but this was not found to occur in the general population [12].

Sleep

Sleep disturbances are reported more frequently in adults with epilepsy than in adults without epilepsy. Increasing evidence suggests that obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS), and sleep maintenance insomnia (difficulty staying asleep) are more commonly found in adults with epilepsy than in those without [19–21]. However, population-based studies on sleep disturbances in patients with epilepsy are lacking. Furthermore, there has been little attention to gender differences in 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%) [22]. This was felt not to be due to any one particular type of sleep disturbance but rather all sleep disturbances were significantly more prevalent in the patients with epilepsy. A prospective Swiss study of 100 adult epilepsy patients found sleep complaints were three times as likely (30% vs. 10%) in a population of people with epilepsy compared with controls [21]. Of those with epilepsy, 52% were found to have sleep maintenance insomnia compared to 38% of controls [21]. In small case series, OSA has been reported in 10% of adults with epilepsy, 20% of children with epilepsy, and approaching 30% in drug-resistant epilepsy patients [19]. Furthermore, OSA is more likely to occur in those who are older, male, overweight, with drug-resistant or late onset epilepsy [19, 20].

More sleep problems are encountered by children with epilepsy than their healthy siblings and other healthy controls [20]. Gender does not appear to contribute to the frequency of problems with sleep in children [20].

Epilepsy in childhood and adolescence

Inheritance and genetics

Several factors have been found to be associated with a predisposition to epilepsy, particularly in families where one member is already affected. Affected children have a greater risk of being born to a mother with epilepsy (2.8–8.7%) compared to a father with epilepsy (1.0 to 3.6%) [23]. How early a parent developed epilepsy also predicts the likelihood of a child developing epilepsy [23]. A parent who develops epilepsy before age 20 has a 2.3–6% risk of their children developing epilepsy, while a parent who develops epilepsy after age 20 has a 1.0–3.6% risk of their children developing epilepsy [23]. Furthermore, in families who have both an affected parent and child, the risk of epilepsy for other siblings increases

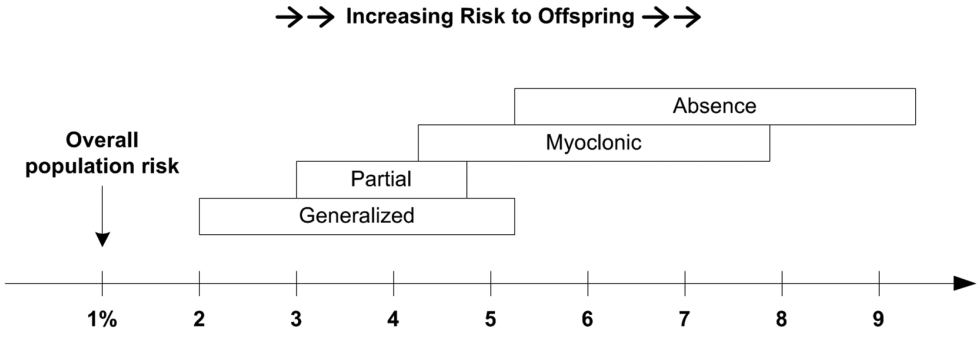

Figure 1.6: Percent of offspring affected with epilepsy. Reproduced with permission from Winawer and Shinnar [23].

from approximately 3% to 8% [23]. 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. The risk of epilepsy in those related to individuals with generalized epilepsy is greater than in those related to individuals with partial epilepsy in some studies; however this has not been observed in all studies (Figure 1.6) [23].

Epilepsy in girls and female adolescents

Gender 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 [24]. Childhood absence epilepsy (CAE) was reported in 2.5% of boys compared to 11.4% of girls in a Norwegian population-based study [25]. Juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) were found to be 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 [8]. JAE was 3 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%) [8]. However, there has been less agreement as to whether gender differences exist in localization-related epilepsies (LRE). While one prospective study of 996 patients with suspected seizures conducted over a 4-year period in Australia reported an equal gender distribution of hippocampal sclerosis (81% in men vs. 79% in women) [26], another retrospective study of 153 patients presenting for pre-surgical evaluation in Germany found that the expression of focal epilepsy due to mesial temporal sclerosis is not the same in females and in males [27]. Females were more likely to experience isolated auras than males (OR, 2.1; 95% CI, 1.1–4.2), and less likely to have secondary generalized 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%). Finally, specific hereditary epilepsy syndromes such as Rett syndrome, Aicardi syndrome, subcortical band heterotopia and epilepsy and mental retardation limited to females (EFMR) are seen primarily in females due to mutations identified in the X chromosome. These syndromes are discussed in detail in Chapter 6.

Catamenial epilepsy

Catamenial epilepsy is defined as a doubling in daily seizure frequency during specific phases of the menstrual cycle [28]. Three categories of catamenial seizure patterns have been described: perimenstrual (C1 pattern), periovulatory (C2 pattern), and entire second half of the cycle (Figure 8.1) in anovulatory cycles (C3 pattern) [28]. Population-based studies exploring the prevalence of catamenial epilepsy are lacking. However, a catamenial pattern was found in 39% of women with LRE in a prospective study of 87 women [29] and 31% of adolescent females in a prospective study of 42 WWE from an Egyptian pediatric neurology clinic [30]. Furthermore, the laterality and focality of epilepsy may play an important role in the ability for reproductive hormones to affect the seizure pattern during the monthly cycle [31].

Epilepsy in childbearing

Fertility and epilepsy

Sexual dysfunction

Population-based studies examining sexual dysfunction in WWE are lacking. However, smaller series have found that WWE are more likely to suffer from sexual dysfunction than WWoE. The epilepsy syndrome and its localization influence sexual function. An American study explored sexual dysfunction in 57 reproductive-aged women on antiepileptic drug (AED) monotherapy recruited from tertiary epilepsy centers compared to 17 WWoE. Lower scores for sexual dysfunction were found in women with primary generalized epilepsy (20.0%) and localization-related epilepsy (20.7%) compared to controls (9%) [32]. Furthermore, sexual dysfunction is seen more frequently in right than left temporal lobe epilepsy (TLE) in both men and women [33].

Another controlled prospective American study of 36 women with TLE recruited from a neurology outpatient service, and 12 controls recruited from the community, examined whether changes in sexual function were found more frequently in women with unilateral TLE [33]. Indeed, sexual function scores were substantially worse with right TLE than left TLE. Additionally, 50.0% of women with right TLE and 30.0% of women with left TLE had sexual dysfunction as compared with 8.3% of WWoE. However, these differences were only significant for those with right TLE [33]. Some AEDs, particularly older, enzyme-inducing AEDs, contribute to sexual dysfunction due to potential influences on the hypothalamic-pituitary-gonadal axis resulting in changes in the levels of hormones supporting sexual behavior (Chapter 9). Enzyme-inducing AEDs are believed to increase sex hormone-binding globulin and thereby decrease bioavailable testosterone which contributes to the emergence of sexual dysfunction [33]. While not statistically significant, 40.7% of WWE receiving AEDs reported increased sexual dysfunction compared to 33.3% of those not receiving AEDs in this same study [33].

Reproductive dysfunction

In WWE, menstrual cycle irregularities, increased risk of infertility, or signs of polycystic ovary syndrome (PCOS) are frequently encountered. Both seizures and AEDs have been causally implicated [34]. Some of the greatest challenges in comparing the results from studies looking at menstrual disorders in WWE are the lack of menstrual disorder definitions, and of population-based studies. Most published studies report data from highly selected, 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%) [35]. In another retrospective American analysis of 100 women with LRE, menstrual disorders were identified by 32% [36]. In a case-control study, 12/36 (33.3%) of WWE compared to 14/100 (14%) community-based WWoE ($p = 0.02$) had menstrual disorders (defined as "abnormal cycle interval, oligomenorrhea, polymenorrhea, increased variability of cycle interval or menometrorrhagia") [37].

Menstrual cycle irregularities, anovulation, higher androgen levels, carbohydrate intolerance with obesity, and polycystic-appearing ovaries are characteristics of PCOS. A lack of a standardized definition of PCOS could explain the varying reported rates in both women with and without epilepsy [38]. Once again, however, there is a lack of population-based studies examining the epidemiology of PCOS in WWE.

In a recent 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. WWE on VPA were 5.46 times more likely to have PCOS when compared to controls (95% CI, 2.23–13.03) [39]. In a recent meta-analysis including 556 WWE treated with VPA, 593 women treated with other AEDs, 120 untreated WWE, and 329 healthy controls, the likelihood of developing PCOS was 1.95 times greater in VPA-treated WWE compared to other AED-treated women [38]. The possibility of developing features of PCOS in those treated with VPA seems to depend on the age at which the female was first treated with VPA [40]. In a prospective American 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 [40].

Another pattern of reproductive dysfunction described in patients with epilepsy is hypothalamic amenorrhea. This is one of the more severe yet common patterns of hypogonadotropic hypogonadism. In one study, 50 women with TLE referred for neurologic evaluation were studied, with 8 (16%) found to have amenorrhea. This is much higher than the expected frequency of 1.5% in the general population [41]. Furthermore, it has been found to occur more commonly in RTLE than LTLE [37, 42]. However, population-based estimates of amenorrhea in WWE have not yet been published.

There are, however, population-based data examining fertility rates in WWE between 1991 and 1995 compared to the 1993 population fertility rates for England and Wales [43]. 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 the WWE in the 25–39 year age group ($p<0{\cdot}001$). In a more recent, prospective cohort of 375 WWE enrolled in an epilepsy and pregnancy registry in India, 38% failed to conceive, with the most important predictors of infertility being multiple AEDs, older age, and lower education [44].

Lower birth rates may be due to lower marriage rates, reproductive dysfunction, fear of birth defects, and concern for an increased risk of epilepsy in the offspring [45]. In a population-based study of 19 American 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 [6]. Similar findings have been

reported in an Indian study of 300 epilepsy patients. Of those with epilepsy (n = 300), 44.6% of women were never married compared to 22.3% of women in the general population (n = 4,687). Of those with epilepsy, 51.1% of women were married compared to 75.7% of women in the general population. Finally, 4.3% of WWE were divorced compared to 2% of women in the general population [46]. Fertility in WWE is discussed in further detail in Chapter 9.

Contraception and epilepsy

It is estimated that nearly half of all pregnancies among WWE are unplanned, similar to the frequency seen in the general population [79]. Contraceptive management in WWE is paramount, due to the possible maternal and fetal complications if contraception fails. Furthermore, the use of enzyme-inducing AEDs can result in birth control failure and contribute to the relatively high number of unplanned pregnancies in WWE [47, 48]. Therefore, preconception counseling to all WWE of childbearing age is necessary.

The prevalence of contraceptive use in 1,630 Dutch women of childbearing age on AEDs was calculated in a study using a population-based pharmaceutical dispensing database [49]. The authors found that only 34.3% of AED users were prescribed highly effective contraceptives compared with 41.2% of the general population of women of childbearing age ($p<.001$). They also found that of WWE who used enzyme-inducing AEDs in combination with a highly effective contraceptive method, 43.5% of them were on an oral contraceptive (OC) containing less than the recommended 50 μg of estrogen. These findings are consistent with a large, population-based study of childbearing WWE on AEDs in the UK. This latter study found that 16.7% of WWE were on OC, and of those on both an enzyme-inducing AED and an OC, 56% were on OC with an estrogen content less than 50 μg [50].

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 [51]. 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 common preconception counseling is for WWE. However, the use of preconception 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 below [52]. A prospective study of 970 pregnancies and 979 offspring in WWE reported a significant correlation between serum folic acid concentrations <4.4 nmol/L and malformations in newborns (adjusted OR, 5.8; 95% CI, 1.3–27) [53]. 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. Prevention of MCMs in offspring of WWE taking AEDs may occur with preconception folic acid supplementation.

The effectiveness of preconception folic acid supplementation was examined in a recent prospective, observational study by looking at the rate of MCMs in a group of women on AED monotherapy in the UK [54]. In the 1,935 cases that received