Original Article

# Women with epilepsy and infertility have different reproductive hormone profile than others

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## Abstract

**Purpose:** One-third of women with epilepsy (WWE) may experience infertility (failure to conceive after 12 months of regular unprotected intercourse). We aimed to compare the hormone profile of WWE and infertility (WWE-I) with that of WWE who had conceived earlier (WWE-F). **Materials and Methods:** In the Kerala Registry of Epilepsy and Pregnancy, we compared the clinical and hormone profile of 50 WWE-I and 40 age-matched WWE-F. Subjects were examined and blood samples were drawn in follicular phase (1-14 days) for 21 WWE-I and 18 WWE-F, in luteal phase (15-30 days) for 23 WWE-I and 15 WWE-F and beyond 30 days for 6 WWE-I and WWE-F who had irregular cycles. **Results:** The two groups were comparable regarding physical, epilepsy syndrome, duration of epilepsy, body mass index, and serum cholesterol levels. Menstrual periods were irregular for 6 WWE-I and 5 WWE-F. The WWE-I group (compared to the WWE-F group) had significantly ($P < 0.01$) higher levels of dehydroepiandrostenedione (2.0 ± 1.7 ug/mL vs. 1.0 ± 0.7 ug/mL) and luteinizing hormone-LH (26.4 ± 37.3 mIU/mL vs. 9.9 ± 14.5 mIU/mL) and lower levels of progesterone (5.2 ± 9.2 ng/mL vs. 10.4 ± 13.4 ng/mL). There was no significant difference in the levels of FT3, FT4, thyroid stimulating hormone, prolactin, follicle-stimulating hormone (FSH), progesterone, testosterone, or androstenedione levels. The WWE-I had 8.5 times higher risk (95% confidence interval 1.2-59.9) of abnormal LH/FSH ratio. WWE who were on antiepileptic drugs (AEDs) (compared to WWE who were not on AEDs) had higher risk of elevated LH/FSH ratio. **Conclusion:** The hormone profile of WWE-I is significantly different from that of WWE-F. These variations need to be interpreted with caution as a causal relationship to epilepsy or use of antiepileptic drugs need to be established through further studies.

## Key Words

Antiepileptic drug, infertility, pregnancy, reproductive endocrine

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## Introduction

Women with epilepsy (WWE) can have reproductive dysfunction[1-5] or lower fertility compared to the rest of the population.[6] Population studies define fertility rate as the number of live births per 1000 women. This definition does not account for the marital status or the pregnancies that do not result in live birth (spontaneous abortion, medical terminations, or intrauterine deaths). In medical parlour, infertility is defined as inability to conceive after 12 months of unprotected regular sexual intercourse. Previous studies have shown that WWE may have increased risk of infertility.[6,7] Epilepsy and seizures may alter the hypothalamo-pituitary-ovarian axis and can lead to derangement of reproductive hormone levels. This is probably due to the involvement of temporal and frontal lobes and hypothalamus that are intimately involved in regulating the reproductive cycle. Ictal and even interictal discharge can also cause reproductive dysfunction.[8] Antiepileptic drugs (AED) s can alter the blood levels of sex steroid hormones produced by the ovaries and adrenal glands.[9] AEDs like phenobarbital (PB) and carbamazepine are powerful inducers of hepatic enzymes involved in the metabolism of sex hormones. AEDs may alter the blood levels of progesterone, estrogen, and other sex hormones and may potentially interfere with reproductive functions.[1] Use of sodium valproate (VPA) had been shown to correlate with the presence of polycystic ovarian syndrome (PCOS).[10] Lower fertility rates could also be due to psychological and social factors. A study in Finland found that persons with epilepsy were less likely to marry and have offspring.[11] Strained family relationships, fear of fetal malformations or aggravation of seizures during pregnancy may be the underlying reason for infertility. The objective of our study was to ascertain the association between infertility and clinical and hormonal profile in WWE. We compared the clinical and reproductive hormonal profile of a group of WWE and infertility (WWE-I) with that of a group of WWE and fertility (WWE-F).

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## Materials and Methods

This study was carried out in the Kerala Registry of Epilepsy and Pregnancy (KREP) program in the Sree Chitra Tirunal Institute for Medical Science and Technology, India. The KREP, operational since 1998, had been recruiting WWE in preconception phase or early pregnancy and had been following them up until their children were 12 years of age.[12,13] A third of the registrations in this registry are WWE who are planning pregnancy (while others are registrations during pregnancy).

For the purpose of this study, we defined infertility as inability to conceive after regular unprotected intercourse for 12 months or more. A regular menstrual cycle of 28 days duration was classified as follicular phase (1-14 days) and luteal phase (15-28 days). Days 13 and 14 were categorized as midcycle phase. Menstrual cycles were classified as regular if cycle length was ≤34 days and irregular if cycle length was 35 days or more. We followed a case-control study design. All WWE enrolled in the registry in the preconception stage who satisfied the following criteria were included (a) Woman should be continuously living with her partner (husband) and aged less than or equal to 40 years at the time of data collection, (b) She or her partner should not be adopting any contraceptive methods, including safe period strategy, (c) She should be having regular unprotected intercourse, and (d) She had failed to conceive even after 1 year of cohabitation as mentioned above. During the period 1998-2011 there were about 1915 registrations. Out of the 1796 registrations in KREP with more than 1 year follow-up, there were 116 eligible candidates who had fulfilled the inclusion criteria. We invited all of them to participate in this study and included the first 50 patients who gave consent for the study (12 declined to participate, 9 were separated from partners, 10 were aged more than 40 years, and 35 persons did not respond or responded too late to our letters). Age-matched controls were drawn from within the KREP who had at least one pregnancy while under follow-up, were non-lactating, and their last pregnancy was 1or more years prior to the examination. This study has the approval of the institutional ethics committee. Written informed consent was obtained from all participants.

All cases and controls were under the regular follow-up of a neurologist with special interest in epilepsy. All those who consented to participate in the study were interviewed with the help of a standard proforma in this Institute between November 2010 and October 2012. We had followed the International League Against Epilepsy classification of epileptic seizures (1981) and epilepsy syndrome classification (1989) in all patients. Clinical history, seizure semiology, electroencephalogram, and imaging findings were taken in to consideration while making the diagnosis. We had documented from the clinical records the treatment of epilepsy with AEDs (date of starting, date of stopping, and reason for stopping, adverse effects, AEDs used in the past), use of folic acid, and any other co medications. Seizure control was ascertained by recall method and recorded on a 6 monthly basis. The comorbidities such as migraine, thyroid disease, systemic disorders, and gynecological conditions if any were recorded. Detailed sexual and reproductive history was obtained for cases and controls. Menarche, cycle characteristics, periods of amenorrhea, last menstrual period (LMP), previous menstrual period, results of pregnancy tests if done were recorded. The reproductive history included, duration of married life, desired number of children, duration of co-habitation, frequency of intercourse, libido, dyspareunia, use of contraceptives in the past, knowledge of fertility period, history of genitourinary infections, pelvic abdominal surgeries, pelvic sepsis, or ectopic pregnancy. All women underwent a detailed physical examination by gynecologist with special emphasis on hormone dysfunction. The examiner recorded hair distribution, breast development, any features of hormone dysfunctions, clitoromegaly, and pelvic examination. Our protocol did not have consent for the examination of the partner or laboratory testing on the partner. We recorded the details of the spouse such as, age, religion, education, occupation, income, previous marriages, fertility in previous marriages, history of medical, surgical issues, smoking, alcoholism, varicocoele, and tuberculosis.

Venous blood samples (6 mL) were drawn for laboratory examination at the time of interview. Blood samples were later classified according to the menstrual phase based on the last menstrual date and cycle length. Samples were drawn in the following phases of menstrual cycle: Between 1 and 12 days (follicular phase) for 15 controls and 17 cases, between 13 and15 days (mid cycle) for 8 controls and 1 case, between 16 and 35 days (luteal phase) for 14 controls and 27 cases. Samples were drawn beyond 35 days from LMP for 3 controls and 5 cases. We analyzed the blood level of luteinizing hormone (LH), follicle stimulating hormone (FSH), androstenedione, dehyroepiandrosterone (DHEA), Progesterone, prolactin, testosterone, FT3, FT4, thyroid stimulating hormone (TSH) by enzyme-linked immunosorbent assay technique. FSH levels higher than 12.1 mIU/mL in follicular phase, >22mIU/mLin midcycle and >12 mIU/mL in luteal phase were considered as abnormal. LH levels >10.5 mIU/mL in follicular phase, >61.2 mIU/mLin midcycle, and >10.5 mIU/mLin luteal phase were considered abnormal. Progesterone levels lower than 4 ng/mLin luteal phase were considered low.

The data were tabulated on a spreadsheet and analyzed with SPSS statistics 17 software. We calculated mean and standard deviation for continuous variables and proportion for other parameters. Group means were compared by *t*-test and proportion was compared with Chi-square test.

## Results

There were 50 subjects with infertility (WWE-I) and 40 WWE in the fertility group (WWE-F) in this study. The age, education, occupation, income, and living standards were comparable for the two groups [Table 1]. The epilepsy syndrome for the WWE-I was classified as generalized epilepsy for 20 (40%) localization-related epilepsy for 30 (60%). The corresponding figures for the WWE-F group were comparable [23 (57%) and 17 (43%)]. The seizure frequency was comparable for both groups. The AED usages for the two groups did not have significant differences [Table 1]. The physical examination did not reveal any difference between the two groups. There was no difference between the two groups with regard to body mass index, fasting blood sugar, lipid profile, hemoglobin levels or FT3, FT4, and TSH levels [Table 1].

**Table 1: Demographic and clinical characteristics of WWE-I and WWE-F**

| Variable | WWE-I | WWE-F |
|---|---|---|
| *n* | 50 | 40 |
| Mean (SD) age in years | 28.2 (4.5) | 29.4 (4.2) |
| Occupation | | |
| Not employed | 33 | 43 |
| Employed | 7 | 7 |
| Age of onset (years) of epilepsy (mean±SD) | 13.4 (6.7) | 13.6 (5.2) |
| Present AED use | | |
| Nil (*n*) | 5 | 6 |
| Monotherapy (*n*) | 32 | 27 |
| Polytherapy (*n*) | 13 | 7 |
| Phenobarbitone (*n*) | 6 | 8 |
| Phenobarbitone mean (SD) dosage (mg/day) | 75 (42.4) | 64.4 (39.6) 6 |
| Phenytoin (*n*) | 4 | 5 |
| Phenytoin mean (SD) dosage (mg/day) | 225 (5) | 280 (109) |
| Carbamazepine (*n*) | 18 | 16 |
| Carbamazepine mean (SD) dosage (mg/day) | 661 (287) | 600 (318) |
| Valproate (*n*) | 14 | 9 |
| Valproate mean (SD) dosage (mg/day) | 625 (376) | 562 (192) |
| Oxcarbazepine (*n*) | 2 | 3 |
| Oxcarbazepine mean (SD) dosage (mg/day) | 750 (212) | 700 (173) |
| Levetiracetam (*n*) | 8 | 1 |
| Levetiracetam mean (SD) dosage (mg/day) | 1312 (530) | 1000 |
| Clobazam (*n*) | 10 | 4 |
| Clobazam mean (SD) dosage (mg/day) | 12.7 (8.3) | 9.25 (6.7) |
| Other AEDs | 6 | 3 |
| Cycles regular | 39 | 35 |
| Cycle irregular | 11 | 5 |
| BMI mean (SD) | 24.3 (3.6) | 26.0 (4.1) |

AED=Antiepileptic drug, BMI=Body mass index, SD=Standard deviation, WWE-I=Women with epilepsy and infertility, WWE-F=Women with epilepsy and fertility

The WWE-I had significantly higher levels of LH than WWE-F. The number of cases analyzed during each phase of the menstrual cycle was small. This difference was significant in the luteal phase of menstrual cycle [Table 2]. The proportion of women with abnormally elevated LH levels was higher for the WWE-I than that for the WWE-F [Table 3]. FSH levels did not differ between the two groups in any phase of menstrual cycles [Table 2].

The LH/FSH ratio was significantly abnormal (higher than 2) for the infertility group [Table 3]. This ratio was significantly abnormal in the follicular phase and luteal phase blood level of prolactin was not different for the two groups [Table 2].

### Ovarian hormones

Blood level of progesterone was significantly lower for the WWE-I when compared to WWE-F. Progesterone level in the luteal phase for those who had regular periods of 28 days was lower than normal (4 ng/mL) for 14 WWE-I (51.9%) and 3 for WWE-F (21.4%), but the difference was not statistically significant.

Serum androstenedione or testosterone levels were not significantly different between the two groups [Table 2]. The DHEA levels were significantly higher for the infertility group when compared to the fertility group.

### AED usage

WWE who were on AEDs (compared to those who were not on AED) had a trend toward increased risk of abnormal LH/FSH ratio (>2). The LH/FSH ratio was high for one (9.1%) of the 11 WWE who were not on AEDs, while it was high for 24 (30.4%) of WWE who were on AEDs. This proportion achieved statistical significance ($P = 0.05$) for the WWE-I group as none of five (0%) who were not on AED had high LH/FSH ratio, while 21 of the 45 (46.7%) who were on AEDs had high LH/FSH ratio.

The proportion of women on VPA in the WWE-I group was not significantly different than that for the WWE-F group. The mean daily dosage of the AEDs for the WWE-I showed a trend towards higher values when compared to that for the WWE-F group [Table 1], but the difference was not statistically significant [Table 2]. Within the infertility group there 14 women who were on VPA (nine with normal LH/FSH ratio ≤2 and five with high LH/FSH ratio >2). This difference was not statistically significant ($P = 0.55$). The dosage of VPA for those with high LH/FSH ratio (660 mg/day) was not significantly different ($P = 0.8$) from that of WWE-I and normal LH/FSH ratio (605 mg/day). With this limited number of samples, we could not establish any association between abnormal levels of reproductive hormones and any specific AED therapy or polytherapy.

## Discussion

The setting of the pregnancy registry provided us a unique opportunity to compare the fertility status and hormone profile for a cohort of WWE. About 10-15% of couples in the community have infertility that can be due to several male and female causes. Our primary objective was not to establish the cause of infertility in WWE. We aimed to compare the hormone profile of WWE according to their fertility status. The key observation in this study is that the reproductive hormone profile of WWE-I differed significantly from that of WWE-F. Our patients had elevated levels of LH, higher frequency of LH/FSH ratio >2, and elevated levels of androgen (DHEA). They also had low levels of progesterone indicating poor functioning of corpus luteum.

Normal ovulatory menstrual cycles are characterized by a follicular phase when the dominant follicle matures under the influence of FSH and produces estrogen that in turn prepares the uterine endometrium for the proliferative phase. The LH levels are low during the early follicular phase, but rapidly increases around days 13 and 14 (LH surge) which is associated with ovulation. The corpus luteum that forms after ovulation goes on to produce progesterone which in turn prepares the uterine endometrium for the secretory phase. Our patients had high levels of LH and abnormally high LH/FSH ratio in

**Table 2: Hormone characteristics of women with WWE-I and WWE-F**

| Variable | WWE-I | WWE-F | *P* |
|---|---|---|---|
| *n* | 50 | 40 | |
| Prolactin (ng/mL) | 22.81 (36.9) | 15.07 (8.17) | 0.197 |
| FSH: all phases (mIU/mL) | 13.14 (24.24) | 11.59 (14.61) | 0.72 |
| LH: all phases (mIU/mL) | 26.4 (37.3) | 9.89 (14.45) | 0.01 |
| Progesterone: all phases (ng/mL) | 5.17 (9.19) | 10.42 (13.36) | 0.03 |
| Testosterone (ng/mL) | 0.708 (0.831) | 0.694 (1.80) | 0.961 |
| Androstenedione (ng/mL) | 1.43 (1.21) | 1.30 (0.98) | 0.592 |
| DHEA (ug/mL) | 1.98 (1.74) | 1.02 (0.74) | 0.002 |
| FT3 pmol/L | 4.15 (.74) | 3.95 (0.64) | 0.199 |
| FT4 (pmol/L) | 11.37 (2.93) | 11.23 (2.81) | 0.825 |
| TSH (uIU/mL) | 2.36 (1.42) | 3.13 (5.9) | 0.393 |

DHEA=Dehyroepiandrosterone, FSH=Follicle stimulating hormone, LH=Luteinizing hormone, TSH=Thyroid stimulating hormone, WWE-I=Women with epilepsy and infertility, WWE-F=Women with epilepsy and fertility

**Table 3: Proportion of WWE-I (*n* = 45) and WWE-F (*n* = 37) with abnormally high level of LH, FSH, and LH/FSH ratio (women with prolonged cycles excluded)**

| | WWE-I [*n* (%)] | WWE-F [*n* (%)] | *P* |
|---|---|---|---|
| LH (high) | | | |
| Follicular phase (1-2 days) | 10 (62.5) | 3 (25) | 0.05 |
| Midcycle (13-14 days) | 1 (100) | 2 (40) | 0.5 |
| Luteal phase (15-28 days) | 7 (33.3) | 2 (15.4) | 0.23 |
| Prolonged cycles (>28 days) | 8 (100) | 2 (22.2) | 0.002 |
| FSH (High) | | | |
| Follicular phase (1-12 days) | 4 (25) | 5 (41.7) | 0.30 |
| Midcycle (13-14 days) | 0 (0) | 2 (40) | 0.67 |
| Luteal phase (15-28 days) | 4 (19) | 3 (25) | 0.5 |
| Prolonged cycles (>28 days) | 1 (33) | 4 (57.1) | 0.5 |
| LH/FSH ratio >2 | | | |
| Follicular phase (1-12 days) | 8 (47) | 1 (6.7) | 0.014 |
| Midcycle (13 -14 days) | 1 (100) | 2 (25%) | 0.33 |
| Luteal phase (15-28 days) | 11 (40.7) | 1 (7.1%) | 0.023 |

FSH=Follicle stimulating hormone, LH=Luteinizing hormone, WWE-I=Women with epilepsy and infertility, WWE-F=Women with epilepsy and fertility

the follicular phase which can interfere with the maturation of follicle. The relatively low levels of progesterone in the luteal phase and high levels of DHEA also point toward the possibility of anovulatory cycles and inadequate luteal function.

Androgens in women come from essentially three sources: Ovaries, adrenal glands, and peripheral adipose tissue. The testosterone measured in the serum is derived mostly from ovaries, while DHEA in the serum is mostly of adrenal origin or peripheral aromatization of estrogen like molecules. In this study, the WWE-I group (compared to WWE-F) had significantly higher level of DHEA and comparable level of testosterone. This pattern of hyperandrogenism, inadequate luteal function, and abnormal LH levels suggest pituitary-ovarian dysregulation and possible anovulatory state. A pattern similar to this occurs with PCOS which is an important cause for female infertility, but can occur in women with normal fertility also.[14] It had been described in WWE[15] and the association between PCOS and VPA and other AEDs is being actively debated.[16] In this study, we could not establish any significant association between use of a given AED and the variation in the hormone profile. A larger study need to be carried out for this purpose.

This is the first study that has profiled the reproductive hormone profile of WWE according to their fertility status and showed an association between infertility in WWE and variation in reproductive hormone profile. Previous studies had shown an association between epilepsy and or use of AEDs with derangement in reproductive hormone profile. The pathophysiology of hormone dysfunction in WWE could be related to the epilepsy and electrical discharges in the brain or the effect of AEDs that are used to treat epilepsy.[13] Our observations have potential clinical implications. These are strong clinical and biochemical signals that the infertility observed in WWE has a biological and hormonal basis. Nevertheless, a causal relationship between the variation in hormone profile and infertility to underlying epilepsy or use of antiepileptic drugs need to be established through further studies. It would be premature at this point of time to implicate hormonal variations as the only mechanism of infertility in WWE. Further, studies involving larger number of couples and more comprehensive clinical and hormonal evaluation are required to unravel this issue.

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## References

1. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. Epilepsia 2003;44 (Suppl 4):11-20.
2. Brodie MJ. Drug Interactions in Epilepsy. Epilepsia 1992;33 (Suppl 1):S13-22.
3. Isojärvi JI. Reproductive dysfunction in women with epilepsy. Neurology 2003;61; (6 Suppl 2):S27-34.
4. Herzog AG. Disorders of reproduction in patients with epilepsy: Primary neurological mechanisms. Seizure 2008;17:101-10.
5. Sahota P, Prabhakar S, Kharband PS, Bhansali A, jain V, Das CP, *et al.* Seizure type, antiepileptic drugs, and reproductive dysfunction in Indian women with epilepsy: A cross-sectional study. Epilepsia 2008;49:2069-77.
6. Sukumaran SC, Sarma PS, Thomas SV. Polytherapy increases risk of infertility in women with epilepsy. Neurology 2010;75:1351-5.
7. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet 1998;352:1970-3.
8. Morrell MJ, Giudice L, Flynn KL, Seale CG, Paulson AJ, Doñe S, *et al.* Predictors of ovulatory failure in women with epilepsy. Ann Neurol 2002;52:704-11.
9. Morrell MJ, Flynn KL, Seale CG, Done S, Paulson AJ, Flaster ER, *et al.* Reproductive dysfunction in women with epilepsy: Antiepileptic drug effects on sex-steroid hormones. CNS Spectr 2001;6:771-2, 783-6.
10. Meo R, Bilo L. Polycystic ovary syndrome and epilepsy: A review of the evidence. Drugs 2003;63:1185-227.
11. Jalava M, Sillanpaa M. Reproductive activity and offspring health of young adults with childhood-onset epilepsy: A controlled study. Epilepsia 1997;38:532-40.

12. Thomas SV, Indrani L, Devi GC, Jacob S, Beegum J, Jacob PP, *et al.* Pregnancy in women with epilepsy: Preliminary results of Kerala registry of epilepsy and pregnancy. Neurol India 2001;49:60-6.
13. Beghi E, Annegers JF. Collaboragive group for the pregnancy registries in Epilepsy. Pregnancy registries in Epilepsy. Epilepsia 2001;42:1422-5.
14. Chang RJ. Polycystic ovarian syndrome and hyperandrogenic states. In: Strauss JF, Barbieri RL, editors. Yen and Jaffe's Reproductive Endocrinology, 6th ed. Phildadelphia: Saunders; 2009. p. 489-516.
15. Joffe H, Taylor AE, Hall JE. Polycystic ovarian syndrome-relationship to epilepsy and antiepileptic drug therapy. J Clin Endocrinol Metab 2001;86:2946-9.
16. Genton P, Bauer J, Duncan S, Taylor AE, Balen AH, Eberle A, *et al*. On the association between valproate and polycystic ovary syndrome. Epilepsia 2001;42:295-304.

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