

“Bane or Boon” for Male Epileptics: Effects of Anti-Seizure Medications (ASMs) on Semen Characteristics

Dear Editor,

Sexual health and fertility issues in male epileptics are not discussed openly considering it a taboo. While prescribing anti-seizure medications (ASMs), emphasis is on female fertility and teratogenicity is often given but male fertility is often ignored. Although with the influence of Western culture, there is some concern raised by young male epileptic patients about their sexual health and fertility issues. Webber MP and coworkers^[1] in their paper a long way back predicted the trends of fertility among people with epilepsy. According to their article, it was found that the fertility rates were one-third to two-thirds lower when compared with the general population. Çubuk C. in their article quoted many clinical studies which reported that hyposexuality and decreased potency are observed in up to 71% of males with epilepsy.^[2] There are various proposed hypotheses by which the semen parameters get altered in males with epilepsy. The exact pathophysiological process is yet to be discovered; however, there are various proposed mechanisms which ultimately culminate into altered semen characteristics and subsequently affect the fertility in male patients. Indian studies are scanty in this aspect of epilepsy. An article previously published in 2021 discussed sexual dysfunction in idiopathic generalized epilepsy. Very scarce data are available on semen characteristics of males with epilepsy from Southeast Asian region, especially countries like India with such a huge burden of epilepsy.

Investigating this further, a cross-sectional study was conducted in the Department of Neurology of tertiary hospital in Northwest India over a duration of 3 years (May 2019–January 2022) with a total diagnosed cases of epilepsy (n = 144). All the patients were males. The mean age of patients was 24.61 years, and the mean duration of illness was 1.87 years. 56 out of 144 (38.8%) patients were married. In these patients, smoking, alcohol drinking, and coffee were not allowed one week before the collection of semen which was obtained by masturbation after 1 week of abstinence. Semen analysis was performed to assess sperm count, motility, morphology, and liquefaction time. The diagnosis of semen abnormalities like azoospermia, oligozoospermia, teratozoospermia, asthenozoospermia, etc., was made according to the WHO guidelines (2010). The data was entered in SPSS 20.0 and was analyzed statistically. The results were surprisingly alarming. Sperm count was significantly lower in focal and other seizure semiology as compared to generalized tonic-clonic seizure group ($P < 0.05$). Prolonged therapy beyond 2 years affects semen liquefaction time, abnormal motility, morphology, and counts adversely ($P < 0.05$). The mean ejaculate volume was found in overall cohort amounting to be

1.1 ± 0.3 ml. Average liquefaction time was 35.67 ± 2.1 mins, and the sperm count was found to be 31.74 ± 1.92 million with the concentration of 10.86 ± 4.18 million per ml. Sperm morphology was also subnormal. Normal forms were seen as 2.34 ± 1.77% only, and mean overall motility was also found to be reduced that was found to be 35.24 ± 1.96%. Monotherapy ASMs had lesser effects on semen as compared to polytherapy drugs. Levetiracetam monotherapy causes the least toxicity, whereas Sodium Valproate monotherapy (18.6% vs. 35.2% patients) causes maximum effects on sperm count, i.e. oligozoospermia among studied drugs. In combination therapy, maximum derangement in semen parameters was seen with Carbamazepine and Sodium Valproate (63.1%) and the least with Levetiracetam and Clobazam (19.11%) ($P < 0.05$). Asthenozoospermia and teratospermia were maximum encountered with Sodium Valproate, whereas least with Levetiracetam.

Various studies done in the past thrown light on the effects of these drugs on male sexual health and fertility. As postulated by Bauer and colleagues,^[3] focal temporal lobe epilepsy itself can lead to testicular failure independent of ASMs' use. Focal epilepsies can propagate to hypothalamus. The reproductive endocrine system may be influenced by the pathophysiological effects of epilepsy as a disease in its own right. Though the complexity, it remains uncertain as to whether hormonal irregularity is because of epilepsy associated hypothalamic-pituitary-gonadal dysfunction or whether it is due to the side effects of antiseizure drugs as discussed by Atif M and colleagues^[4] in their review article. SS Chen and coworkers^[5] described the effects of long-term antiseizure drug therapy on sperm motility. They found significantly decay rate in sperm motility in patients with epilepsy as compared to healthy controls. However, this study was done *in vitro* which was not the case in our study. Various other studies conducted in past by MS Yerby and coworkers,^[6] T Hayashi *et al.*^[7], and X Xiaotian *et al.*^[8] also revealed that drugs such as Phenytoin, Sodium Valproate, and Carbamazepine cause abnormal sperm morphology, reduced motility, lower sperm count, and reduced testicular volume as a side effect of long-term therapy. In their case report, MS Yerby and coworkers^[6] described how a patient on Sodium Valproate can have very low sperm count (<50,000/ml), 100% asthenozoospermia, <10% viability, and 100% teratozoospermia. Our study also found oligozoospermia (35.6%), asthenozoospermia (42.9%), teratozoospermia (49.34%) in patients on Sodium Valproate monotherapy. Hayashi *et al.*^[7] observed that switching two patients from Sodium Valproate to Phenytoin, as discussed in their case report, can potentially reverse oligoasthenozoospermia. In our study, patients were not

followed up and effect of drug switching could not be assessed over a period of time. X Xiaotian *et al.*^[8] observed that both Sodium Valproate and Levetiracetam have effect on sperm motility (25–50% reduction) and cause teratozoospermia, the effects being more pronounced with the former drug. Findings of our study stand in coherence with these. The latest study by Tallon E and colleagues^[9] concluded that VAL causes potentially reversible infertility. T Hayashi *et al.*^[10] also reported that long-term exposure to Carbamazepine causes asthenozoospermia. The present study also found asthenozoospermia in 20.22% of patients receiving this drug as monotherapy.

Our study had limitation in the form of small sample size. The results cannot be generalized to larger population. The patients were not followed up, and final outcome could not be assessed on the basis of single assessment as done in the present study.

In conclusion, epilepsy and ASMs have effects on the fertility and semen characteristics of men with epilepsy either alone or in combination. While prescribing antiseizure drugs to a male in the reproductive age group utmost care should be taken about the effect of drug as significant changes occur in semen parameters which can pose fertility issues. Moreover, this study can add to the existing literature and opens further possibilities of research in this aspect of disease.

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Conflicts of interest

There are no conflicts of interest.

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