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Review article

Maternal and neonatal complications during pregnancy in women with epilepsy

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ABSTRACT

Epilepsy is the commonest serious neurological problem faced by obstetricians and gynaecologists. Epidemiological studies estimate epilepsy to complicate 0.3–0.7% of all pregnancies.[1,2] The importance of epilepsy in pregnancy lies in the fact that many women with epilepsy (WWE) have to go through their pregnancy while taking antiepileptic (AED) drugs. Both the seizures and AEDs can have harmful effects on the mother as well the foetus. Thus, during pregnancy, the clinician faces dual challenge of controlling seizures as well as preventing teratogenicity of AEDs.[1] In this review we discuss the possible impact of seizures as well as AEDs on mother as well as the child. We try to answer some of the commonest questions which are relevant to successful management of pregnancy and ensuring birth of a healthy baby.

1. Is the incidence of obstetrical complications during pregnancy increased in WWE?

Several studies[1,2] have evaluated the incidence of obstetrical complications in WWE. In 1973, data from Norwegian Birth Registry was published.[3] It reported that WWE have high risk of low for birth weight babies, greater neonatal mortality, pre-eclampsia, bleeding during pregnancy and induction of labour. However it did not comment on use of AEDs. In 1985, Yerby and colleagues[4] compared pregnancies in 204 WWE with 612 women without epilepsy using Washington State birth certificates. They found an increased risk of pre-eclampsia [odds ratio (OR): 2.45; 95% confidence interval (CI: 1.17–5.51)], previous foetal loss (OR: 2.66; CI: 1.01–6.98), caesarean delivery (CD) (OR: 1.93; CI: 1.31–2.83), induction of labour (OR: 4.29; CI: 1.77–10.39), low birth weight (OR: 2.79; CI: 1.35–5.74), and low APGAR score at birth (OR: 3.74; CI: 1.57–8.88). However, several other studies[5–8] did not find any increase in obstetrical complications in WWE. Specifically from India, results of Kerala pregnancy registry[9,10] have shown increased frequency of anaemia, ovarian cysts, uterine fibroid and spontaneous abortions in WWE. They also found higher incidence of hypertension and pre-eclampsia in WWE on AEDs. For WWE not on AEDs, risk of CD is slightly increased but risk of other obstetrical complications is not increased. In 2009, American Academy of Neurology[11] concluded that the risk of CD or late pregnancy bleeding in WWE on AEDs is not substantially (>2 times) increased. They concluded a possible moderately increased (>1.5 times) risk of CD in WWE on AEDs and a substantially increased risk (>2 times) of premature contractions or delivery or labour in WWE on AEDs who also smoke. They also stressed on lack of evidence to suggest increased risk of pregnancy induced hypertension, eclampsia or spontaneous abortions in WWE.

Borthen et al.[12] compared 942 births in WWE with full National cohort of women without epilepsy and found high risk of gestational hypertension and pre-eclampsia. In same study they also compared 205 deliveries in WWE with 205 age and parity matched women without epilepsy delivering on the same date. They found increased risk of bleeding per vaginum (OR: 6.4; CI: 2.7–15.2) and pre-eclampsia (OR: 5; CI: 1.3–19.9). The risk of pre-eclampsia was even higher with lamotrigine (OR: 7.5; CI: 1.4–39). The risk of severe pre-eclampsia existed regardless of presence or absence of seizures during pregnancy, but was observed only in AED users. In another study[13] same group compared 2805 pregnancies in WWE with 362,303 normal pregnancies. They found a higher rate of postpartum haemorrhage (OR: 1.2; 95% CI: 1.1–1.4), induction of labour [OR: 1.3; CI: 1.1–1.4], Caesarean section (OR: 1.4; CI: 1.3–1.6) and preterm delivery in WWE. These rates were

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even higher for WWE using AEDs, with ORs (CIs) of 1.5 (1.3–1.9), 1.6 (1.4–1.9) and 1.6 (1.4–1.9) respectively. For WWE not using AEDs, there was only a slightly increased risk of CD. In another study[14] on 49 WWE, there was increased risk of vaginal bleeding in late pregnancy (OR: 1.9; CI: 1.1–3.2), preeclampsia (OR: 1.8; CI: 1.3–2.4), premature delivery (before 34 weeks of gestation) (OR: 1.5; CI: 1.1–2.0) and gestational hypertension (OR: 1.5; CI: 1.0–2.2) in WWE on AEDs compared to WWE not taking AEDs. The rates of these complications were similar in WWE not on AEDs and general population. In one recently published study, the risk of death during delivery was more than 11 fold higher in WWE compared to women without epilepsy. In same study, WWE were also found to have a higher risk of CD, preterm labour, stillbirth and pre-eclampsia.[15] These studies confirm an increased risk of obstetrical complications in WWE, though the overall risk is low.

1.1. Conclusions

Although most WWE have uncomplicated pregnancies and normal babies, they do face certain difficulties. WWE usually need AEDs during pregnancy to remain seizure free. However, AEDs during pregnancy pose a certain risk to mother as well as developing foetus. WWE do have an increased risk of preterm birth, bleeding, pre-eclampsia and CD. The risk of these complications is maximum in women taking lamotrigine during pregnancy followed by carbamazepine.[16]

2. What is the risk of seizures during pregnancy and what is their impact on pregnancy and delivery?

2.1. Control of seizures during pregnancy

Harden et al.[11] reported that if WWE were free from seizures for at least 9 months before conception, the chance of freedom from seizures during pregnancy was 80–90%. These findings suggest that physiological changes during pregnancy generally do not affect threshold for seizures. In 2013, EURAP study (a prospective study from 42 countries studying 3784 pregnancies in WWE),[17] reported that 66.6% of WWE remained seizure free during pregnancy. The seizure frequency was increased in 17.3% and decreased in 15.9% of WWE. The proportion of seizure free women was lower in women receiving lamotrigine (58.2%), compared to valproate (75%), carbamazepine (67.35%) and phenobarbital (73.4%). Similarly risk of generalized seizures was more in lamotrigine group. The chance of recurrence of seizure was higher when oxcarbazepine was used as monotherapy. Seizures occurred in 3.5% of women during labour. Thomas et al.,[18] studied 1297 pregnancies in WWE and reported that 47.5% of WWE remain seizure free during pregnancy. In their cohort, most robust predictors of occurrences of seizures during pregnancy were occurrence of seizures before pregnancy and polytherapy with AEDs. In this study, occurrence of seizures in pre-pregnancy month was associated with 15 fold higher risk of seizures during pregnancy and generalized seizures tended to occur during the first trimester. In both the above studies,[17,18] risk of seizures during delivery was related to prior frequency of seizures. Also, the risk of seizures during pregnancy in WWE is lower in women with planned pregnancies compared unplanned pregnancies. WWE with planned pregnancies also had a lower likelihood of change in their AED regimen during pregnancy.[19]

2.2. Risk posed by seizures to pregnancy

The immediate effects of seizures on foetal well being are difficult to quantify as developing foetus is not accessible to study.[20] Regarding partial seizures, it is generally accepted that while simple partial seizures without loss of awareness have little impact on foetus, maternal seizures with loss of awareness (complex partial seizures) may be associated with foetal bradycardia as indicated by two case reports.[21,22] However eventually both these ladies delivered healthy children. Generalized seizures, on the other hand, are associated with trauma as well as alterations in electrolytes, oxygenation and blood pressure, all of which may affect the developing foetus, a fact which is confirmed on animal studies.[20] With regards to effects of generalized seizures on human foetus, one has to resort to extrapolation of data from obstetric studies where eclamptic seizures are shown to be associated with foetal heart changes such as bradycardia, transient decrease in heart rate at peak of uterine contractions and decreased variability of baseline foetal heart rate.[23] These foetal heart parameters revert back to normal in 3–10 min following termination of seizures and are likely related to seizure induced maternal hypoxia. A few studies have evaluated effect of seizures on human foetus. Minkoff et al.[24] reported a case of foetal death due to intracranial hemorrahge in utero as a consequence of maternal seizure. Rauchenzauner et al.[25] reported that children born to WWE who experience >1 generalized tonic clonic (GTC) seizure during pregnancy have five times higher preterm risk, shorter gestational age (SGA) and low birth weight (LBW). Cumming et al.[26] reported a higher risk of neurodevelopment defects in women experiencing >5 GTC seizures during pregnancy. Similarly in another study,[27] it was found that valproate therapy, occurrence of more than 5 GTC seizures and lower maternal IQ during pregnancy were associated with a seven point reduction in verbal IQ in children. In the landmark EURAP study,[17] status epilepticus occurred in 1.8% (convulsive in 33% of these) of pregnancies. There were no maternal deaths and miscarriage though there was one stillbirth. Another study from Taiwan[28] showed that seizures during pregnancy increased risk of SGA babies in WWE. As this study included only WWE not taking AEDs, results of this study are unique as there are no confounding effects of AEDs. Thus current available data attests to the common belief that seizures during pregnancy are associated with harmful effects on foetus.

2.3. Risk of death in WWE during pregnancy

Adab and colleagues[27] reported a 10 fold higher mortality during pregnancy in WWE, which is higher than the reported standard mortality rate due to epilepsy in general population. Edey et al.[29] reported WWE to account for 14 deaths among 2,291,493 maternities. Out of these, 11 were due to SUDEP (sudden unexplained death of epileptic patient). One death occurred while bathing, one was secondary to hypoxic brain damage and one was due to chest trauma during a seizure followed by secondary sepsis. Nine deaths occurred in women using lamotrigine, out of whom seven used lamotrigine as monotherapy. Maternal mortality rate in WWE is 100/100,000 compared to overall rate of 11/100,000. Thus risk of death in WWE is 10 folds higher than normal women. However, risk of SUDEP in WWE is expected to be lower than general population as SUDEP is more prevalent in patients with intractable epilepsy and women with intractable epilepsy are less likely to get pregnant.[20]

2.4. Seizures and delivery

WWE have increased risk of complications during delivery. In EURAP study,[17] seizures complicated 2.6% of deliveries in women on lamotrigine and carbamazepine, 1.9% of deliveries on phenobarbital and 1.4% of deliveries in women on valproate. In Kerala registry, risk of seizures was found to be maximum during the three day peripartum period.[18] In this study; several women were

either not on AEDs or on low doses of AEDs. Thus, it is imperative that all the women take AEDs during labour at usual periods.[18,20]

2.5. Conclusion

There is evidence from case studies that seizures do have a harmful effect on the developing foetus. Women with untreated epilepsy have higher risk of having children with growth retardation and cognitive dysfunction. Risk of seizures during delivery is low and epilepsy per se is not an indication for CD. Risk of seizures during pregnancy may be decreased by careful preconceptional planning.

3. What is the influence of type of AED on risk of major congenital malformations (MCMs) in babies born to WWE?

Ever since Meadow SR[30] reported increased risk of cleft lip, cleft palate and other abnormalities in children born to women taking primidone, phenobarbital or phenytoin, several studies have not only confirmed the higher incidence of birth defects among children born to WWE on AEDs, but also broadened the spectrum of developmental toxicity, including adverse effects on cognitive and behavioural development.[31–35] Tomson and Battino,[36] in a pooled analysis of 26 studies, found risk of major congenital malformation (MCM) to be 6.1% in children born to WWE on AEDs compared to 2.8% in WWE not on AEDs and 2.2% in normal women. Similar results were reported by Fried et al.[37] who in their meta-analysis reported a higher risk of MCM in offspring of WWE on AEDs; while the risk in WWE not on AEDs was similar to that in general population. These studies confirm that exposure to AEDs in utero is associated with increased risk of MCMs.[38]

The commonest MCMs include cardiac defects, facial clefts and hypospadias in that order with some dependence on the type of AED used. Cardiac defects are the commonest MCMs associated with exposure to phenytoin, barbiturates, carbamazepine and lamotrigine while most common MCMs associated with exposure to valproate include neural tube defects.[38] The incidence of MCMs with different AEDs when used as monotherapies is shown in Table 1. Though there is some difference across various registries, use of valproate is associated with maximum incidence of MCMs. MCM rates are minimal with levetiracetam followed by lamotrigine/carbamazepine while MCM rates with phenobarbital are in between valproate and lamotrigine/carbamazepine. The exact prevalence of MCMs following use of levetiracetam, oxcarbazepine and topiramate is still unknown because of low rates of exposure and even lesser is known about gabapentin, pregabalin, zonisamide and lacosamide.[38] Several studies[43,45] and a recent review[39] suggest that with currently available data, levetiracetam and lamotrigine have emerged as safest drugs during pregnancy.

3.1. Monotherapy versus polytherapy

The risk of MCMs is more when WWE receive polytherapy during pregnancy.[40] The risk is maximum when valproate is included in the polytherapy regimen. The risk of MCM in NAARP (North American AED pregnancy Register) was 9.1% when lamotrigine and valproate were given together compared to 2.9% when lamotrigine was combined with some other AED. The

Table 1
Percentage of major congenital malformations (MCM) with commonly used AEDs as monotherapy in various registries.[37]

Valproate monotherapy					
Registry	Cardiovascular defects	Orofacial clefts	Hypospadias	Neural tube defects	Any MCM
EURAP[38]	2.18%	0.4%	1.68%	1.09%	9.7%
NAAPR[39]	2.5%	1.1%	3.1%	1.2%	9.3%
UK-Ireland[40–42]	1.1%	1.2%	1.2%	0.2%	6.7%
Carbamazepine monotherapy					
EURAP	1.57%	0.14%	0.64%	0.36%	5.6%
NAAPR	0.29%	0.48%	0.19%	0.29%	3%
UK-Ireland	0.8%	0.2%	0.3%	0.2%	2.6%
Phenobarbital monotherapy					
EURAP	2.76%	0.46%	0.46%	0.46%	7.4%
NAAPR	2.5%	2%	0.97%	0	5.5%
Lamotrigine monotherapy					
EURAP	0.63%	0.16%	0.31%	0	2.9%
NAAPR	0.19%	0.45%	0	0.13%	1.9%
UK-Ireland	0.4%	0.1%	0.5%	0.1%	2.3%
GSK-international[43]	0.61%	0.11%	0.11%	0.17%	2.2%
Levetiracetam monotherapy					
NAAPR	0.22%	0	0	0.22%	2.4%
UK-Ireland	0	0	0	0	0.7%
Phenytoin monotherapy					
EURAP	–	–	–	–	5.8%
NAAPR	–	–	–	–	2.9%
UK-Ireland	–	–	–	–	3.7%
Oxcarbazepine monotherapy					
EURAP	–	–	–	–	3.3%
NAAPR	–	–	–	–	2.2%
UK-Ireland	–	–	–	–	5.9%
Topiramate monotherapy					
EURAP	–	–	–	–	6.8%
NAAPR	–	–	–	–	4.2%
UK-Ireland	–	–	–	–	4.3%

EURAP: international registry of antiepileptic drugs and pregnancy; NAARP: North American AED Pregnancy Registry; UK-Ireland: UK and Ireland Epilepsy and Pregnancy Register; GSK International: GlaxoSmithKline International Lamotrigine Register.

risk was only 1.9% when lamotrigine was used alone.[44] Similarly The incidence of MCMs was 15.4% when carbamazepine was compared with valproate, compared to 2.5% when carbamazepine was combined with AED other than valproate and 2.9% when carbamazepine was used as monotherapy.[46] In contradictions to previous belief where polytherapy was thought to be associated with high risk of MCMs, recent data suggest that polytherapy regimens based on lamotrigine or carbamazepine are associated with similar rates of MCMs as monotherapy.[47]

3.2. Dose dependency of MCMs

Risk of MCMs becomes high with higher doses of the AEDs used. In EURAP,[40] the lowest rate of MCMs was observed with lamotrigine < 300 mg/day (2%), carbamazepine < 400 mg/day (3.4%) and valproate <700 mg/day (5.6%) at time of conception. The risk of MCM with a valproate dose of >1500 mg daily was 24.6%.[47] NAARP[41] reported lowest MCM rates (<5%), when median average daily dose of valproate was 500 mg during the first trimester. However, NAARP did not find dose effect relation with any other AED. The UK and Ireland register[42] reported a significant increase in risk of MCM with increase dosage of valproate and carbamazepine and nonsignificant increase with lamotrigine. The incidence of MCM was 5% with ≤600 mg valproate daily, 1.9% for ≤500 mg carbamazepine daily and 2.1% for ≤200 mg lamotrigine daily. All these results stress on need to administer lowest possible dose of AED during pregnancy.

3.3. Risk of recurrence of MCM after a prior birth with MCM in WWE

There is still no consensus on the risk of MCM in future pregnancy following a pregnancy resulting in a child with MCM. While United Kingdom and Australian pregnancy registries have documented increased risk of recurrence of MCM in subsequent pregnancies following a pregnancy with MCM, results of Kerala pregnancy registry suggest no increase in risk. However there were some differences between these studies such as the type of population, methodology as well as dosage and type of AEDs. The dosage of AEDs specifically valproate and carbamazepine was approximately 50–65% in Kerala pregnancy registry compared to the other two registries. Thus, it is likely that exposure to lower dose of AED may not be associated with high risk of MCM in pregnancies following a prior MCM, while high dose of AED may be associated with an increased risk. These observations advocate use of lowest possible dose of AEDs in subsequent pregnancies following a prior childbirth with MCM.[48]

3.4. Genetic susceptibility for MCMs

Current evidence suggests existence of a strong genetic susceptibility for teratogenic effects of AEDs. Parental history of MCM is strongly associated with increased risk of MCM in WWE (OR-4.4).[40] In Australian Register,[49] risk of a child having MCM in 2nd pregnancy is 35.7% in WWE on AEDs with history of MCM in first pregnancy. For women on valproate risk is up to 57.2%. In UK pregnancy Register,[50] the risk of having MCM in 2nd child was 16.8% if there was MCM in first child. While these observations, as discussed in previous section, may just be related to dosage and type of the AEDs used, these do suggest existence of genetic susceptibility for development of MCM in WWE. One recent study evaluated role of polymorphisms in genes encoding for cytochrome enzymes responsible for AED metabolism, in causation of MCM in WWE. In this study it was found that presence of ABCB1 Ex07 + 139 C/T genotype in WWE was significantly associated with occurrence of MCM in children. Similarly, there was significantly higher presentation of Cyp2C19 poor metabolizer allele *2 and genotype *2*2 in WWE having children with MCM compared to WWE with normal children. There was however no relation between type of MCM and these genotypes. These observations do suggest a role for genetic susceptibility in development of MCM in children born to WWE on AEDs.[51]

3.5. Conclusion

There is substantial increase in risk of MCMs in children born to WWE on AEDs. The maximum risk of MCMs is associated with use of valproate both as monotherapy and polytherapy. Risk is relatively lower with lamotrigine, levetiracetam and carbamazepine. The risk of teratogenicity becomes higher at high doses of AEDs. The data of teratogenicity of newer AEDs is limited. The limited data suggests that while levetiracetam has lower risk, the risk associated with topiramate is greater than carbamazepine or lamotrigine. In contradiction to previous beliefs, the risk of MCMs with regimens employing 2 or more AEDs is same as that with monotherapy regimens especially when valproate and topiramate are not used as part of polytherapy regimens.

4. Does in utero exposure to AEDs cause cognitive dysfunction?

There is enough evidence from animal studies that exposure to several AEDs (phenobarbital, phenytoin, valproate, carbamazepine, lamotrigine) in utero is associated with cognitive dysfunction. Though preliminary data suggests levetiracetam to be safe, it is limited and future research is warranted in this regard.[52] In addition, several studies have evaluated cognitive dysfunction in children born to WWE on AEDs.

With regards to carbamazepine, a large prospective study found that in utero exposure to carbamazepine is not associated with any evidence of cognitive dysfunction at school age. In another study, it was found that children born to WWE on carbamazepine had a better IQ than valproate and did not differ significantly from either lamotrigine or phenytoin when assessed yearly from 3 to 6 years of age.[34,53,54] Regarding risk of autism spectrum disorders (ASD) in children exposed to carbamazepine in utero, the results are controversial with one study suggesting an association and others refuting such an association.[52]

Adab and its colleagues[27,55] reported a lower IQ and need for education support in children exposed to valproate in utero compared to other AEDs. A recent meta-analysis[56] found mean verbal IQ to be lower by 7–11 points in children born to WWE on valproate compared to other AEDs. The cognitive dysfunction is apparent in valproate exposed children from an early age and it persists into the school going years.[34,57,58] This risk appears to be related to dose of valproate. Mean IQ in children exposed to doses of 1000 mg or more is 10 point lesser for children exposed to lower doses.[34] Though administration of folate during conception resulted in a higher eventual IQ in one study,[34] replication of this findings is required in other studies. With respect to ASD, while Christensen et al. reported a prevalence rate of 4.2% for children exposed in utero to valproate, other authors have estimated a prevalence of 8%.[52]

The data regarding effects of lamotrigine on cognitive function in children is sparse. Two studies[26,57] did not find any difference in cognitive functions of children born to WWE on lamotrigine. Two other studies[34,54] found that cognitive functions of children born to WWE on lamotrigine was significantly better than valproate, but similar to carbamazepine and phenytoin. With regards to dosage of lamotrigine, which is more likely to result in cognitive dysfunction, further data is needed to draw any conclusion. Regarding ASDs, while two studies[35,54] did not find any increased incidence of ASDs, one study[53] did find occasional occurrence on autistic traits in

children born to mothers treated with lamotrigine during pregnancy.

Only two studies[59,60] have assessed effects of levetiracetam on cognitive abilities on children. The cognitive functions of children born to WWE on levetiracetam were similar to general population. Also in rodent models, levetiracetam is found to be the only antiepileptic drug which does not induce apoptosis in rat pups brain even when given in combination with a drug known to induce apoptosis.[47] Future research is urgently needed before any conclusion regarding safety of levetiracetam in pregnancy is drawn.

4.1. Conclusion

The mean IQ of children born to WWE on valproate is 7–11 points lower as compared to health children. The cognitive effects of valproate are dose dependent with better outcomes at a dose of <1000 mg daily. Levetiracetam appears to be the safest drug with regards to cognitive dysfunction in children born to WWE on AEDs.[47]

5. Does intrauterine growth retardation (IUGR) occurs in children born to WWE?

Several studies[31,33,61,62] have reported evidence of IUGR in form of LBW, reduced head circumference and being SGA in children born to WWE both on AEDs (carbamazepine, topiramate and polytherapy) and not on AEDs. Farmen et al.[63] evaluated IUGR in foetuses of WWE. The frequency of SGA babies and low ponderal index was highest in WWE exposed to lamotrigine (18.2% and 19% respectively), followed by carbamazepine (14.8% and 14.3% respectively).

5.1. Conclusion

AEDs are associated with IUGR. Further studies need to be done to find risk associated with individual AEDs.

6. Future directions

Several studies are going on to delineate risks posed by epilepsy to WWE and their children. MONEAD[64] (Maternal and neurodevelopmental outcomes of in utero antiepileptic drug exposure) is one such ongoing prospective observational study by Emory University. This study has stopped recruiting patients and results are expected by end of 2017. Main aims of this study are (a) to determine if frequency of seizures, CD and depression is increased during pregnancy in WWE, (b) to determine neurobehavioral, language and cognitive functions of children born to WWE and (c) to determine neonatal outcomes in WWE. In addition, it also aims to determine if breastfeeding by WWE on AEDs could adversely affect cognitive abilities of children. Once published, the results of this study are supposed to provide data regarding efficacy and side effect profile of AEDs in WWE including the newer ones such as levetiracetam and lamotrigine. One unique feature of this study lies in the fact that all the patients had undergone measurement of AED blood levels as well as area under the concentration time curves. Thus, this study may provide insights regarding relationship between blood levels of AEDs and adverse maternal as well as foetal outcomes.

7. How to plan for pregnancy in WWE?

1. All WWE should be counselled regarding the possible teratogenic effects of AED. They should receive information regarding the frequency and expected type of MCMs associated with their treatment regimen. These should be reassured that most WWE will have normal pregnancy and delivery. [Level D] For instance if a WWE on valproate is planning pregnancy, she should be given information about the risk of neural tube defects and it should be discussed whether valproate needs to be changed taking into account all the factors such as response to treatment, response to previous drugs, and history of MCM in a prior child etc. All WWE should also be told that 2% of pregnancies in general population results in children having MCMs and that no one can guarantee birth of a child without MCM.
2. Every attempt should be made to achieve good seizure control in WWE, especially generalized convulsions. The patient's current seizure frequency (particularly GTC seizures) should be reviewed. If seizures are uncontrolled, consider alteration in treatment regimen taking into account potential teratogenicity of chosen AEDs. If patient's seizures are well controlled, consider withdrawal of drugs if the risk of recurrence is low and patient is willing to take the risk [Level D].
3. Try to avoid valproate/phenobarbital if possible during the first trimester [Level C]. If possible try to avoid valproate as part of polytherapy regimens [Level B]. If either of these has to be used, try to use the lowest effective dose [Level B].
4. Obtain history of MCM in prior pregnancies and in family. If positive, explain the high risk of MCMs, consider genetic testing and switching over to drugs which were not used in prior pregnancies as well as monitor the future pregnancies more intensely for any evidence of MCMs.
5. Give 5 mg folic acid supplementation daily [Level C].
6. Make all possible adjustments in AED regimen and ensure a stable regimen before conception [Level C].

8. How to care for pregnancy in WWE?

1. Continue folic acid during pregnancy [Level C].
2. Continue same AEDs in same dosage until there is poor seizure control or unacceptable side effects of AEDs [Level D].
3. Avoid withdrawal of AEDs during pregnancy [Level D].
4. Obtain a high level ultrasound at 14–18 weeks of pregnancy for detailed view of foetal structures. If a malformation is identified, the couple should be counselled about the possible effects of malformation on baby. The decision regarding continuation or termination of pregnancy should be taken after detailed discussion with the parents [Good clinical practice].
5. All seizures occurring in pregnancy may not be epilepsy. Whenever in doubt evaluate for the cause of seizures and manage accordingly [Good clinical practice].
6. Whenever seizures occur late in pregnancy, possibility of eclampsia should be considered and if deemed appropriate, proceed with delivery induction [Good clinical practice].
7. All newly born children should be administered 1 mg vitamin K intramuscularly [Level D].
8. The key to successful outcome lies in a team approach (preferably a separate clinic) consisting of obstetrician, neurologist and neonatologist for preconception counselling as well as antenatal and postpartum care (Level U).

Authors' contribution

R. Bansal and G. Jain involved in data collection, drafting of manuscript, review of literature. P.S. Kharbanda, M.K. Goyal and Vanita Suri involved in concept, drafting the article and manuscript revision.

Conflicts of interest

The authors have none to declare.

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