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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

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