

## CASE REPORTS

# Risk of malformation with combination of lamotrigine and low dose clonazepam for juvenile myoclonic epilepsy in pregnancy: A case report

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### Abstract

Conventional anti-epileptic drugs (AEDs) are known to have higher potential to induce fetal birth defects when administered to pregnant women with epilepsy. However, data on the influence of newer AEDs on the outcome of pregnancy is limited. Several national and international level epilepsy and pregnancy registries have been created to facilitate reporting. This is the case report of a pregnant woman with juvenile myoclonic epilepsy taking a combination of lamotrigine and clonazepam, who delivered a still birth with multiple fetal anomalies. This indicates the need to build teratovigilance data base.

### INTRODUCTION

Pregnancy registries have been activated in Europe, North America, Australia and India, to enroll women with epilepsy receiving anti-epileptic drugs (AEDs) to be monitored prospectively to study the outcome of pregnancy.<sup>1</sup> Five registries and one large prospective study have recently summarized results with lamotrigine (LTG) and have provided information on the incidence of malformations on LTG polytherapy with valproate.<sup>2</sup>

LTG, a phenyl triazine derivative developed as an anti-folate agent, is most widely used as a second generation AED. However, its anti-seizure activity is reported to be voltage and use dependent inactivation of sodium and voltage gated calcium channels, explaining its efficacy in focal and primary generalized seizures including absence seizures. LTG is also known to decrease synaptic release of glutamate and is primarily used as add on therapy, but is also used as monotherapy for partial seizures. Adult dosage is 100-300 mg/day.<sup>3</sup> The adverse effects include dizziness, headache, diplopia, nausea, somnolence and skin rash.<sup>4</sup> LTG clearance is reported to increase markedly throughout pregnancy and hence monthly monitoring of concentrations is recommended. Fetal malformations of extremity, cardiac, dysmorphic facial features, co-anal atresia, upper

respiratory and gastrointestinal anomalies have been reported with use of LTG in pregnancy<sup>5</sup> due to its extensive transplacental transfer.<sup>6</sup> Clonazepam (CZP), a benzodiazepine, enhances GABA mediated inhibition and is primarily used as adjunctive treatment in myoclonic and atonic seizures. Adult dosages is 0.5-10 mg/day, with dose limiting adverse effects that include sedation, ataxia and behavioral changes such as depression.<sup>7</sup> Its pharmacokinetic profile and fetal effects in pregnancy are yet to be established.

Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epileptic syndrome characterized by myoclonic jerks, generalized tonic-clonic seizures, and sometimes absence seizures. JME is said to represent 5-11% of all epilepsy cases with estimated incidence of approximately 1 per 100,000 population, and prevalence of 10 to 20 per 100,000. The clinical presentation is characteristic, but misdiagnosis and its attendant treatment delay are frequent.<sup>8</sup> Sodium valproate is claimed to be the most effective first line AED in men with JME. In women, because of risk of teratogenicity and side effects of weight gain and polycystic ovarian disease, LTG is recommended by some as a preferred AED. CZP is considered as an add-on medication during seizure exacerbations. Its prolonged use is however reported to be inappropriate.<sup>9</sup>

Despite the fact that AEDs are known teratogens, the primary goal in management of patients with epilepsy is directed at complete seizure control.<sup>2</sup> Risk of major fetal malformations in mothers with epilepsy is 3-6% without AEDs, 4-8% with AEDs, compared to 2-3% in the general population. The factors that may contribute include AED dose and polytherapy.<sup>1,7</sup> Incidence of major malformations increases disproportionately with the number of AEDs; approximately 3% with one drug, 5% with two drugs, 10% with three drugs and > 20% with more than three AEDs.<sup>7</sup> Several mechanisms have been proposed to be implicated in teratogenicity of first generation AEDs. However, the underlying mechanisms of teratogenic effects of LTG or CZP are uncertain. This is the case report of a woman with JME taking LTG and CZP during pregnancy, who delivered a still birth with fetal anomaly.

### CASE REPORT

A 27 year old female, known case of JME since the age of 17, was initially on treatment with sodium valproate, 200 mg/day for 7 years. She got married at the age of 24 and conceived soon after, but had a spontaneous abortion at two and half months in Aug 2006. At that time she was on valproate 200 mg/day. She conceived again in June 2007 and was on LTG 150 mg/day. At the time of conception, she had occasional myoclonic jerks and suffered from lack of sleep, hence the dose of LTG was increased to 175 mg/day. She delivered a full term normal baby girl in Feb 2008. The baby was alive and healthy when last reported. Three weeks after delivery she complained of sleep deprivation and increase in jerks. The dose of LTG was therefore increased to 250 mg/day. As there was not much improvement in her sleep pattern and frequency of myoclonic jerks, a small dose of CZP 0.25 mg/day was also added.

In August 2008, she conceived for the third time. She was on combination of LTG 250 mg/day and CZP 0.5 mg/day. This dosage regimen was continued for the next 5 months. As no seizures were reported during that period, the dose of CZP was reduced to 0.375 mg/day. During the seventh month of pregnancy the dose of CZP was further reduced to 0.25 mg/day. On 14<sup>th</sup> March, 2009 at 35 weeks of gestation, patient felt only feeble fetal movements. When she reported to the hospital the following day, the fetal heart beat was absent. On 17<sup>th</sup> March 2009, following induction of labor, she gave birth to a still born baby. The new born was diagnosed to have non immune hydrops fetalis, resulting in intrauterine

death. On examination, the baby had ascitis and polydactyly (Figure 1). During this pregnancy patient did not give any history of seizures and had received folic acid 5 mg/day, from preconception till delivery. In addition, patient gave past history of leukocytoclastic vasculitis. Her family history revealed that her father was a diabetic and mother hypertensive. All her antenatal investigations were within normal limits except for the ultra sonogram done on 15<sup>th</sup> March 2009, which showed fetus at 33 weeks gestation with ascitis and pleural effusion. A fetal autopsy was conducted which showed hydrops fetalis and polydactyly.

Pathological examination of fetus showed gross morphological changes with polydactyly of all four limbs, cardiovascular anomalies including transposition of great vessels, patent foramen ovale and ventricular septal defect. There was also evidence of amniotic fluid aspiration in the lungs.

### DISCUSSION

Data from the international pregnancy registry has examined the effect of 1<sup>st</sup> trimester LTG monotherapy on frequency of MBDs up to a daily dose of 400 mg. However, above that dose the data is scarce to allow accurate estimates of fetal risk. The UK epilepsy and pregnancy registry reported a statistically higher frequency of major birth defects among first trimester LTG monotherapy exposures at doses > 200 mg/day.<sup>10</sup> An interim report from International Antiepileptic Drugs and Pregnancy Registry, submitted in May 2009 on 6,443 prospective cases including one-year follow-up at birth showed 22/1,136 pregnancies with AED polytherapy who received combination of LTG and CZP. Of the 1,136 pregnancies, 8.4% had one or more birth defects as compared to 289 out of 4,819 (6%) pregnancies with AED monotherapy. Outcome in relation to exposure to individual drugs or specific drug combinations is presently being analyzed by this registry.<sup>11</sup> The LTG Pregnancy Registry Interim Report (1<sup>st</sup> September 1992 through 31 March 2009) was released in July 2009. Fifty-six patients had 1<sup>st</sup> trimester exposure to LTG with CZP. Three were reported to have spontaneous abortions and two induced abortions. There were 49 live births of which two had birth defects. One had hydrocephalopathy, muscle spasticity and arterio venous fistula. This patient was on LTG 200 mg/day, preconception till 6 weeks of gestation, with CZP 1 mg/day preconception and throughout pregnancy. The second baby had hypospadias



Figure 1. New born baby showing polydactyly.

where mother had received LTG preconception 200 mg/day, and 100 mg/day, till unknown week of gestation with CZP preconception and during 1<sup>st</sup> trimester. As a part of the same registry in March 2009, 159 pregnancy outcomes involving birth defects were reported retrospectively. There were two patients on LTG-CZP combination. One had corpus callosum agenesis and colpocephaly documented by MRI, while the other had Pierre Robin syndrome, butterfly vertebra and hypoplastic iliac crest.<sup>12</sup> The limitation of these studies is that they were observational and not randomized clinical trials.

In the present case report the fetus was still born, with various anomalies. While the role of other risk factors cannot be ruled out, it is likely that LTG with CZP are important in causing the birth anomalies. However, further observational studies involving the use of such combinations and the influence of their dosage range on the outcome of pregnancy needs to be carried out. Therefore, in women with epilepsy during pregnancy, careful risk benefit assessment should be done before prescribing or maintaining newer AED therapy. The general approach should include monotherapy as far as possible, lowest but optimal doses of AED for adequate seizure control, and regular AED level monitoring when available. In addition to such preventive strategies, prompt reporting system should form an essential part of teratovigilance programs to guide future practices.

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