RESULTS OF A MULTICENTERED REGISTRY OF OXCARBAZEPINE EXPOSED PREGNANCIES

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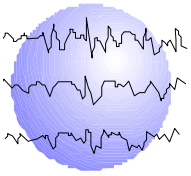

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REVISED ABSTRACT

RATIONALE: Women with epilepsy (WWE) who are of child bearing age face the difficult decision of either 1) taking an AED with potential teratogenic effects, or 2) risking increased seizures which may threaten the pregnancy if no or lesser amounts of AED are taken. Experience with the newer AEDs is accumulating. Oxcarbazepine was first released in 1990 in Denmark and 2000 in USA. Exposures continue with unclear information regarding safety for the fetus. The present registry information reports the experience to date with OXC in our centers.

METHODS: Over 20 epilepsy programs in the USA were asked to participate. Six centers participated. Each mother signed informed consent before completing a survey with the local investigator. Data were sent to 1 site for analysis and included maternal health and reproductive history; seizure history; AED use and seizure occurrence during the pregnancy; folate and prenatal vitamin use; ultrasound results; complications during the pregnancy; Apgar scores and delivery complications; gestational age; infant malformations; breast-feeding.

RESULTS: Six centers provided data for a total of 29 pregnancies: 27 retrospective and 2 prospective. Mothers were 19-38 years old (mean age =27.4, median=27) with epilepsy onset from 0.25-31 years of age. Mean OXC doses increased through trimesters from a mean daily dose at conception of 1336 mg/day to 1891 mg/day at delivery. 55% were on monotherapy. Ten patients (38%) were seizure free throughout; 6 had only simple partial ± complex partial seizures. 93% of all patients who had seizures during pregnancy had seizures in 1st and 2nd trimesters, 38% in 3rd, and 8% at delivery. Ultrasounds were abnormal in 4 (1 oligohydramnios, 2 polyhydramnios, 1 small for gestational age). 74% delivered vaginally. There were 2 fetal losses and 1 preterm delivery. Apgars were >7 and 9 in all reported. Hypospadias was the only malformation reported, occurring in one infant exposed to monotherapy. 93% received folate (mean dose 2.4 mg) and prenatal vitamins. Maternal complications reported were 2 hyperemesis, 1 preeclampsia, 1 bed rest, 1 elevated GTT, 1 fall, 1 1st trimester bleeding, 1 depression. 62.5% reported breast-feeding. Reported data was insufficient to assess infant development.

CONCLUSION: Collection of experience with OXC during pregnancy is still limited. Malformation rates appear to be comparable to reported rates for pregnancies in WWE with other AEDs or without therapy. In this multi-centered experience additional pregnancies support the statement that mothers taking OXC during pregnancy have successful outcomes with AED mono or polytherapy.

INTRODUCTION:
Women with epilepsy (WWE) who are of child bearing age face the difficult decision of 1) taking an antiepileptic drug (AED) with potential teratogenic effects, or 2) risking increased seizures which may threaten the pregnancy if no or lesser amounts of AED are taken. Experience with the newer AEDs is accumulating. Oxcarbazepine (OXC) was first released in 1990 in Denmark and 2000 in USA. Exposures continue with unclear information regarding safety for the fetus. The present registry information reports the experience to date with OXC in our centers.

METHODS:
Over 20 epilepsy programs in the USA were asked to participate. Six centers responded and five contributed data. Data were collected and analyzed at one site. IRB approval was obtained from a central IRB or a local IRB if required by the institution. Each mother signed an approved consent before completing a survey administered by the local investigator. Data included maternal health and reproductive history, seizure history, AED use and seizure occurrence during the pregnancy, folate and prenatal vitamin use, ultrasound results, complications during the pregnancy, apgar scores, delivery complications, gestational age, infant malformations, and breastfeeding experience.

RESULTS
Data was collected between February 2005 and December 2006. Twenty-nine pregnancies were collected: 27 retrospective and 2 prospective. Data were not complete for all parameters.

Maternal demographics are described in Table 1. Table 2 presents the characterization of the pregnancies. First trimester exposure to OXC occurred in 86% and 96% had third trimester exposure. Fifty-five percent were on monotherapy. No patients were on more than three AEDs. Four had OXC added in the third trimester while one mother had OXC discontinued. OXC dose increased between the first trimester and delivery in 56%, the increase ranging from 8 to 225% (mean 88%, median 43%). (See Table 3)

Ultrasounds were abnormal in 4 (1 oligohydramnios, 2 polyhydramnios, 1 small for dates). Seventy percent delivered vaginally and 2 of these were breech presentations. There were two fetal losses (at 8 weeks and 14 weeks) and one preterm delivery. Initial apgar scores were >7 and 9 at subsequent evaluation in all reported births (n=11). Hypospadius was the only malformation reported and occurred in OXC monotherapy (3.7%). Mothers received folate (93%) and prenatal vitamins (86%). Maternal complications included 1 hyperemesis, 3 pre-eclampsia, 1 gestational diabetes, 1 1st trimester bleeding, 1 maternal fall, and 1 maternal depression. Breast feeding was successfully accomplished in 62.5%. Data was insufficient to assess infant development.

Seizures increased over baseline frequency in 28%, decreased in 22% and remained unchanged in 50%. Table 4 describes the seizure outcomes for the population.

CONCLUSION:

Experience with OXC during pregnancy continues to occur. Malformation rates and seizure outcome in this multi-centered experience are comparable to reported rates for pregnancies in WWE with other AEDs or without therapy. The exposed fetal numbers are , however, still small even when added to other reported experiences[1,2,3,4]. Caution and close neurological and obstetrical follow-up is recommended, including following serum levels throughout the pregnancy and adjusting daily doses to compensate for increased clearance. This reported experience supports the statement that mothers taking OXC during pregnancy have successful outcomes in either mono- or polytherapy.

References:

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Table 1

Maternal Demographics

N	29

Age at Pregnancy	Mean = 26.7 yrs.	Range = 19-38 yrs.
Age at Seizure Onset		Range = 25-31 yrs.

Seizure Type	**N**	**%**
Simple Partial	14	48
Complex Partial	22	76
Secondary Generalized	20	69
Generalized	0	

	N	**%**
Prior Pregnancies	38	
Vaginal Delivery	23	60
Unknown	1	3
Malformation	0	
Fetal Loss	14	37
Spontaneous Abortion	*11*	*79*
Ectopic Pregnancy	*1*	*7*
Induced Abortion	*1*	*7*
Fetal Loss with Seizure	*1*	*7*

Table 2

Pregnancy Results

Ultrasound	**N**	**%**
Normal	17/21	81
Abnormal	4/21	19

Delivery	**N**	**%**
Vaginal	20	74
C-Section	7	26
Fetal Loss	2	7
(miscarriage at 14 wks, intrauterine death at 8 wks)		

Complications*	**N**	**%**
Oligohydramnios	2	7
Polyhydramnios	2	7
Preeclampsia	3	11
Hyperemesis	1	3
Breech	2	7
Failure to Progress	1	3
Maternal Depression	1	3
Bleeding in 1st Trimester	1	3
Seizure at delivery	2	8

	N	**%**
Vitamin K Supplementation	19	70

	N	**%**
Folate Supplementation	18	62
Mean dosage (range)	2.4 mg/day	(0-4 mg/day)

	N	**%**
Prenatal Vitamins	25	86

Gestational Age	38.9 weeks (34-40)

	N	**%**
Breast Feeding	15	60

	N	**%**
Infant Malformation (hypospadias)	1	4

*statistics excluded 2 pregnancies with fetal loss in first trimester

[a]data points not available for all patients for all parameters

Table 3

Exposure to Oxcarbazepine (OXC)

Maximum OXC Dose	mg/day	(range, mean)
1st Trimester	2400	(0-2400, 1207)
2nd Trimester	3000	(0-3000, 1656)
3rd Trimester	3900	(0-3900, 1620)

Co-AED	N	%
None	16	55
Polytherapy*	13	45
VNS	2	7

	N	%
Seizure during pregnancy	17	61
Seizure free during pregnancy	11	39

*CBZ 2, PHT 1, LTG 3, TPM 2, PB 1, PGB 1, Benzo 1

Table 4

Seizures During Pregnancy

Overall Seizure Frequency During Pregnancy	%
Increased	28
Decreased	22
No Change	50

Seizure Free Prior to Pregnancy	
Remain Seizure Free	64
Breakthrough seizure	36

Seizures Prior to Pregnancy	
Seizure free during pregnancy	11
Seizures during pregnancy	89

Seizure Free Throughout Pregnancy	38
Seizure in 1st Trimester	52
Seizure in 2nd Trimester	42
Seizure in 3rd Trimester	38
Seizure at Labor and Delivery	8