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Congenital malformations in infants exposed to antiepileptic medications in utero at Boston Medical Center from 2003 to 2010

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ABSTRACT

Objective: The aim of this study was to determine the frequency of association of major congenital malformations in pregnancy in women exposed to antiepileptic drugs (AEDs) in an inner city population.
Background: Approximately 0.3–0.5% of all pregnancies involve women with epilepsy. The risk of congenital malformations associated with AED therapy has been well documented, ranging from 2 to 10% as compared to a rate of 3% in the general population. However, the risk of these occurring in a higher risk population, such as an inner city tertiary care center, with multiple comorbidities is not as well known.
Design/methods: Using the Boston Medical Center Database between the years 2003 and 2010, a list of all infants born with major congenital malformations (MCMs) to mothers on AEDs was compiled. Major congenital malformations were defined as cleft lip and/or palate, ventricular or atrial septal defect, other cardiac malformations, and urogenital defects. During pregnancy, AED exposure including serum levels, other medication exposures, breakthrough seizure frequency, positive toxicology tests, and other maternal comorbidities were also analyzed.
Results: Of 17,246 live births between 2003 and 2010, 330 of those births demonstrated a MCM (malformation rate of 1.91%). Of those births, 64 mothers had epilepsy and were exposed to AED therapy during pregnancy, accounting for 0.37% of all births during this time period. Overall, three pregnancies in women with epilepsy resulted in a baby with a MCM, accounting for a 4.7% malformation rate in this patient population. In mothers on AEDs for other indications, the MCM rate was slightly higher, 5.0%, and in women on benzodiazepine monotherapy during pregnancy, the rate was quite high, 10.6%.

1. Introduction

Pregnant women with epilepsy account for 0.3–0.5% of all pregnancies, corresponding to 25,000 newborn children each year in the USA alone [1,2]. With the increasing use of antiepileptic medications (AEDs) for other indications, such as psychiatric conditions and chronic pain, the number of women on AEDs during pregnancy is likely to be much higher [1]. The risk of major congenital malformations (MCMs) attributed to AEDs varies, ranging from 2 to 10% depending on specific medications used, which can be significantly higher than that of the general population without AED exposure, approximately 2–3% [3–5]. The teratogenic effects of AEDs can occur when taken in any trimester, typically with structural defects associated with first trimester AED exposure and cognitive sequelae as a result of AED exposure in the third trimester [6].

Based on past data, first generation AEDs, such as phenytoin, carbamazepine, phenobarbital, and valproic acid, among others, are being used less during pregnancy than the second generation antiepileptic medications [6–10]. Elucidation of the risks of specific AEDs is complicated by the fact that people with epilepsy have an increased risk of other medical comorbidities, including psychiatric disorders and endocrinological disorders [11]. Since approximately 4.5% of women are exposed to antidepressants during pregnancy, the potential for polypharmacy may further increase the risk of MCMs in women with epilepsy [12,13].

The risk of congenital malformations occurring in a higher risk population, such as an inner city tertiary care center, with multiple comorbidities is less clear. In an attempt to assess these unknown risks, a retrospective analysis of offspring born in an inner city tertiary care center exposed to AEDs was performed.

2. Materials and methods

Using the Boston Medical Center Database, between the years of 2003 and 2010, a list of all infants born with major congenital

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malformations (MCMs) to mothers on AEDs was compiled. During pregnancy, AED exposure including serum levels, other medication exposures, breakthrough seizure frequency, positive toxicology tests, and other maternal morbidities were also analyzed. Women on AEDs were divided into those with epilepsy and those with psychiatric conditions without epilepsy.

This study was retrospective, observational in nature, and approved by the Boston University School of Medicine Institutional Review Board. Our primary objective was to determine the rate of major congenital malformations in offspring exposed to AEDs in utero. Secondary objectives included determining the frequency of exposure to specific AEDs during pregnancy, frequency of maternal comorbidities, and frequency of AED exposure for any indication.

Each mother's chart was analyzed for the presence of a seizure disorder, seizure frequency, and the use of AEDs during pregnancy. Specific AED exposures, serum AED drug levels, concomitant medications, and comorbidities such as psychiatric disorders with or without the use of psychotropic medications were analyzed. Each offspring's chart was analyzed for the presence of MCM with both ICD-9 code and chart review.

Major congenital malformations were defined as cleft lip, cleft palate, ventricular septal defect, atrial septal defect, and urogenital defects. Other documented malformations that were not considered to be major malformations were cardiac and included patent foramen ovale, peripheral pulmonary stenosis, patent ductus arteriosus, ventricular hypertrophy, and ventricular dysfunction among others. Antiepileptic drug medication compliance was determined based on repeated serum levels, if possible, urine toxicology screens, and patient report.

3. Results

3.1. General population—infant malformations

There were a total of 17,246 live births at Boston Medical Center between 2003 and 2010. Of these, there were 330 live births with congenital malformations (preterm and light for dates diagnoses were excluded) for a malformation rate of 1.91%, as compared to the rate of 3% in the general population [3]. Thirty-three of these 330 live births with MCMs had more than one congenital malformation. The total rate of congenital cardiac malformations nationwide was documented to be 81.4 out of 10,000 live births in 2008, with ventricular septal defects being the most common congenital cardiac malformations [14]. However, as seen in Table 1, atrial septal defects were more common than ventricular septal defects in our population between 2003 and 2010. The frequency of genitourinary defects such as hypospadias was concordant with national data. Midline facial defects, such as cleft lip/palate, were rarer at our institution as compared to the general population. A full comparison of malformation rates in our patient population as compared to the available national data can be found in Table 1.

3.2. Women with epilepsy and AED exposure

At Boston Medical Center, 204 women gave birth to live infants who were exposed in utero to AEDs, regardless of an epilepsy diagnosis. Overall, 11.7% of women were on 1st generation AEDs during pregnancy as compared to the remaining 88.3% on newer AEDs. Thirty-one point nine percent were exposed to polypharmacy during pregnancy. Sixty-four infants were born to women with a diagnosis of epilepsy, accounting for 0.37% of live births in our patient population.

Of the 64 women with epilepsy who gave birth during this time period, 7 had diagnoses of epilepsy or a seizure disorder on chart review and had a documented MCM. One of these women had an unclear history of seizures and was on AEDs for multiple psychiatric diagnoses. Two women were not on AEDs during their pregnancy and one woman was poorly compliant with AEDs in pregnancy (per recorded serum levels, there was minimal in utero exposure to AEDs). Of the remaining three women, all had well-documented exposure to AEDs during pregnancy without multiple comorbidities, and had infants diagnosed with what are considered major congenital malformations. See Fig. 1 for full details of these individuals. This resulted in a MCM rate in women with epilepsy (WWE) on AEDs during pregnancy of 4.7% in our patient population. The major malformations noted were 1 case of hypospadias and two cases of ASDs.

Of the women with epilepsy and subsequent major congenital malformations, 2 of the 3 were seizure-free during their pregnancy; seizures in the third woman were quite difficult to manage during pregnancy. One of the three was considered to be “advanced maternal age” or over 35 years old at the time of pregnancy. Two of the three women were on older AEDs (phenytoin and valproic acid), and the other was on a newer medication (lamotrigine). Two of the three were managed with monotherapy. Of note, the woman who was not seizure-free during pregnancy and who was on polytherapy had an infant with multiple malformations and congenital issues including the abovementioned ASD, microcephaly, dysmorphic features, dystonia, and exotropia among others.

3.3. Women with AED exposure for any indication

Of note, there were 140 women in our patient population who were exposed to AEDs (including benzodiazepines) for reason besides seizure control. Indications for AED use included psychiatric indications, neuropathy, and headaches. Antiepileptic drugs used included lamotrigine, gabapentin, oxcarbazepine, valproic acid, and clonazepam. Of those, 7 women delivered infants with MCMs for a malformation rate of 5.0%. Malformations noted included ASD, VSDs, and cleft lip/palate. Within the 7 women without epilepsy on AEDs and with MCMs, medications used during pregnancy included clonazepam, valproic acid, and lamotrigine. Five of the seven women were on clonazepam and no other AED. Overall, 47 pregnant women were on benzodiazepines only in terms of AEDs between 2003 and 2010 for indications including anxiety, substance abuse, and other psychiatric indications. Therefore, there was

Table 1
Frequency of major congenital malformations at BMC 2003–2010 in comparison to the general population:.

Type of malformation	Number of patients (of 17,246 live births)	BMC malformation rate	National malformation rate[a]
VSD	97	5.62 in 1000 births	2.75 in 1000 births [14]
ASD	155	9 in 1000 births	1.03 in 1000 births [14]
Cleft lip	<6	–	–
Cleft palate	6	0.347 in 1000 births	0.635 in 1000 births [15]
Cleft lip +/− palate	7	0.4 in 1000 births	1.064 in 1000 births [15]
Hypospadias & epispadias	76	4.41 in 1000 births	3–5 in 1000 births [16]
Total	330[b]	19.8 in 1000 births	30 in 1000 births [3]

[a] Rates of malformations were taken from different sources.
[b] Includes 10% of patients with multiple MCMs.