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Maternal and fetal outcomes associated with vagus nerve stimulation during pregnancy

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ABSTRACT

Objective: To access the effect of vagus nerve stimulation (VNS) on the outcome of pregnancy.
Methods: We used the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and its network to search for women receiving adjunctive VNS during pregnancy. Data on maternal and fetal outcomes were extracted from the registry databases and outcomes were evaluated.
Results: Twenty-six pregnancies were identified in 25 women. All women were exposed to a relative high VNS stimulation level (mean duty cycle 18%, range 5%–51%). Most women had seizures during pregnancy and almost 70% were on antiepileptic drug (AED) polytherapy. The proportion of women with obstetrical interventions was 53.9% (95% confidence interval [CI] 33.4%–73.4%) which was higher compared to the EURAP average (48.2%; 95% CI 47.2%–49.1%).

One infant (3.9%; 95% CI 0.1%–19.6%) was born with a major malformation (unilateral congenital glaucoma), which is within the range expected among offspring of AED-treated women.
Conclusion: Although the present series of VNS-exposed pregnancies is the largest reported to date, the sample size is insufficient to draw any firm conclusions on the safety of VNS in pregnancy but the findings suggest an increased rate of obstetrical interventions, and no clear signal of VNS-related teratogenicity.

1. Introduction

Vagus nerve stimulation (VNS) has been used as adjunctive therapy for drug-resistant epilepsy and depression for more than 20 years but even though more than 90,000 stimulators have been implanted worldwide (data on file 2016, LivaNova, Houston, TX) very little is known about the influence of VNS on pregnancy and fetal outcomes.

One small animal study in ten rabbits failed to demonstrate any teratogenic effects or other abnormalities that could be attributed to VNS (Danielsson and Lister, 2009). In humans, a total of nine cases of VNS in pregnancy have been published and all were reportedly associated with healthy babies (Ben-Menachem et al., 1999; Galbarriatu et al., 2015; Houser et al., 2010; Husain et al., 2005; Kalayjian and Heck, 2005; Salerno et al., 2016). The delivery mode was specified in three of these cases with obstetrical interventions reported in two of the deliveries (n = 1 caesarean section, n = 1 induced labor). One pregnancy was complicated by mild pre-eclampsia and post-partum uterine atony and hemorrhage (Houser et al., 2010).

The mechanisms of action of VNS are not fully understood, but appear to involve modulation of synaptic activity and, thereby, cortical excitability in widespread regions of the brain (Henry, 2002; Krahl and Clark, 2012), including components of the central autonomic system such as the hypothalamus. Therefore, VNS therapy may, at least theoretically, influence neuroendocrine activity and affect pregnancy

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Table 1
Maternal and fetal outcome data.

Case no. (Maternal age, years)	Maternal AEDs	Mode of delivery	Gestational age at birth, weeks	Apgar score 1 min/5 min	Birth weight, grams	Major malformation
1 (dm)	PHT,VPA,CNZ	Caesarean section	dm	dm/dm	4800	None
2 (28)	CBZ,CNP,LEV,PB	Normal	36.6	dm/dm	dm	Yes
3 (31)	LTG	Caesarean section	38.4	9/10	2700	None
4 (34)	LTG, CLO	Normal	39.5	8/8	3630	None
5 (29)	LEV, TPM	Caesarean section	37.2	dm/dm	2400	None
6 (37)	CBZ, CNP	Caesarean section	40.5	dm/dm	3680	None
7 (24)	CBZ, TPM	Vacuum extraction	40.5	9/9	3220	None
8 (28)	LTG, CLO	Caesarean section	37.4	9/9	2810	None
9 (32)	LEV, LTG	dm	38	10/10	4270	None
10 (29)	CBZ	Normal	39.3	10/10	3000	None
11 (30)	CBZ, VPA, ZNS	Induced delivery	40	10/10	3050	None
12 (29)	CBZ, LTG	Caesarean section	38.3	6/8	2970	None
13 (31)	LEV, CLO	Induced delivery	39	8/9	3425	None
14 (32)	LTG	Normal	40.4	dm/dm	3050	None
15 (29)	LTG	Abortion				
16 (33)	LEV	Normal	38.3	8/10	3100	None
17 (36)	LTG, CLO	Normal	dm	dm/dm	dm	None
18 (30)	CBZ,LEV,LCM,PB	Caesarean section	35	4/5	2200	None
19 (33)	LTG	Caesarean section	38	8/9	3880	None
20 (31)	CBZ, LEV	Normal	38	8/10	dm	None
21 (31)	CBZ	Normal	40.1	9/9	3030	None
22 (dm)	CBZ	Normal	dm	dm/dm	dm	None
23 (dm)	LTG, CLO	Vacuum extraction	dm	dm/dm	dm	None
24 (dm)[a]	LEV, LTG	Caesarean section	36	dm/dm	dm	None
25 (dm)[a]	LEV, LTG	Caesarean section	39	dm/dm	dm	None
26 (dm)	VPA, GBP	Normal	dm	dm/dm	dm	None

Abbreviations;: dm, data missing; AED, antiepileptic drug; CBZ, carbamazepine; CLO, clobazam; CNZ, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

[a] Pregnancies from the same woman.

physiology and fetal development. A study in non-pregnant rats has also demonstrated that efferent vagal stimulation can influence uterine blood flow and contractions (Sato et al., 1996). This raises the possibility of VNS-induced activation of vagal efferent fibers altering uterine functions during pregnancy and delivery, although, to our knowledge, this has not been investigated.

Here, we report a series of 26 pregnancies followed-up prospectively in 25 women with epilepsy being treated with VNS. These pregnancies were identified through the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and its network.

2. Methods

The EURAP registry is an international observational cohort study established in 1999 and designed to determine the comparative risk of major congenital malformations after prenatal exposure to antiepileptic drugs (AEDs). The registry relies on the collaboration of investigators from more than 40 countries from Europe, Asia, Australia, and Latin America and per March 2016 more than 22,000 pregnancies have been entered into the database. The details of the EURAP study methodology were published previously (Tomson et al., 2011).

We first used the EURAP database to search for pregnancies in women receiving VNS. However, because the EURAP database focuses on AED exposure, information on VNS treatment is not a mandatory part of the case report form and some VNS-exposed pregnancies might have been missed in the initial search. Therefore, all national coordinators of the EURAP network were personally contacted and asked to report additional cases of maternal VNS treatment not identified in the database. Pregnancies with maternal use of VNS that were exclusively registered in the Australian and UK pregnancy registries were also included (Campbell et al., 2014; Vajda et al., 2016).

Data on maternal and fetal outcomes were extracted from the registry databases. Information on the VNS device used during pregnancy was collected separately through contact with EURAP reporting physicians. Data used in the analysis included maternal data (age at conception, epileptic syndrome, changes in seizure frequency and AEDs during pregnancy), obstetrical outcomes (gestational week at birth and mode of delivery), fetal outcomes (1 and 5 min Apgar score, gestational weight at birth and malformations), and VNS settings (output current, signal time, frequency, on/off time). VNS stimulation time (duty cycle) was calculated by dividing the stimulation time by the sum of the stimulation on and off time.

Rates and means with 95% confidence intervals [CIs] were used. The multicenter registry protocols were approved by the ethical committees of participating centers and informed consents from women identified outside the registries were obtained.

3. Results

3.1. Maternal data

A total of 29 pregnancies in women on VNS treatment were identified. Of these, 14 were registered in the EURAP database, five in the UK registry database, and one in the Australian registry database. Nine pregnancies were reported separately by EURAP national coordinators or reporting physicians (Czech Republic n = 3, Denmark n = 1, France n = 1, Spain n = 4). The four Spanish cases included have been reported by others (Rodríguez-Osorio, in press). Three pregnancies were excluded, two because it was not confirmed that the stimulator was activated throughout pregnancy, and one because the outcome data had been already published (Salerno et al., 2016). Therefore, 26 pregnancies were available for final analysis, including one twin birth.

Among the 25 women analysed, three had idiopathic generalized epilepsy, 17 had focal epilepsy, and five had unclassified epilepsy or missing information. Maternal age at conception was specified in 21 cases (mean 31 years; range 36.7–24.7 years).

In four cases information of seizure activity was missing. Only one woman was reported seizure-free throughout pregnancy. Four had