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Experience on the use of Vagus Nerve Stimulation during pregnancy

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ABSTRACT

Objective: Vagus Nerve Stimulation (VNS) is a neuromodulation device approved for the treatment of medically refractory epilepsy. Worldwide, only 35 cases of pregnancies that has been described. This study aims to continue to increase the limited knowledge of the use of VNS during pregnancy.
Methods: We interrogated the database of the Epilepsy program at Western University (1998–2018), and identified those patients who were implanted with VNS and became pregnant.
Results: From 114 patients implanted with VNS in our centre, four patients had a total of seven pregnancies. This is the first report with one woman implanted with VNS having three pregnancies. Three patients had genetic generalized epilepsy and one focal epilepsy due to periventricular nodular heterotopia. The median duration since implantation was 3.17 years (IQR: 1.33–4.33) and the output was 2.75 mA (IQR: 1.5–3.5). No modifications in stimulation settings were made in any patient during pregnancy. Three patients had obstetric complications, requiring c-sections. All babies were healthy, except one with intellectual disabilities of unclear severity.
Conclusion: Our small sample suggests VNS could increase the obstetrical complications, but is likely safe for the fetus. However, a larger sample size should be collected to determine safety and potential teratogenicity of VNS.

1. Introduction

Approximately 3.53 out of 1000 women of childbearing age have epilepsy in Canada and 0.3-0.5% of all pregnancies occur in women with epilepsy (Heather Gilmour et al., 2016). As in the general population, it is expected that 20–30% will have drug resistant epilepsy (DRE)[1], requiring several antiepileptic drugs (AED)[2] . The combination of several AED increases the risk of teratogenicity on the fetus and an increased risk of obstetrical complications (Mawer and Liverpool and Manchester Neurodevelopment Group, 2010). However, seizures can also have terrible hypoxia-related consequences for the mother and the fetus (Christensen et al., 2018).

Vagus Nerve Stimulation (VNS)[3] is a type of neuromodulation device designated for the treatment of DRE usually reserved for those who are not candidates for resective epilepsy surgery. Since the approval of VNS 20 years ago in North America, more than 90,000 patients have been implanted worldwide (data on file 2016, LivaNova, Houston, TX). VNS is a relatively safe therapy with a small number of complications and side effects.

Since the first VNS was implanted, less than 40 cases of pregnant women with VNS have been published (Sabers et al., 2017; Rodríguez-Osorio et al., 2017). This is a small number in relation to the total number of fertile women implanted with VNS. Hence, it is important to evaluate the efficacy and safety of VNS in women during pregnancy. The risk of congenital malformations, obstetric complications and possible cognitive outcomes in newborns must also be investigated.

The aim of this study is to describe our experience with the use of VNS on women during pregnancy who have DRE.

2. Method

From the database of the Epilepsy program at Western University in London, Ontario (1998–2018), we identified 114 patients implanted with VNS. Of those patients, four patients fulfilled the inclusion criteria and had a total of seven pregnancies.

The study protocol was approved by the ethics committee at the London Health Sciences Centre/Western University and followed the Declaration of Helsinki code of ethics.

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[1] DRE: Drug resistant epilepsy.
[2] AED: Antiepileptic Drug.
[3] VNS: Vagus Nerve Stimulation.

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Table 1
Maternal features and fetal outcome.

	Patient 1		Patient 2	Patient 3			Patient 4
	Pregnancy 1	Pregnancy 2		Pregnancy 1	Pregnancy 2	Pregnancy 3	
Age	24 y-o	27 y-o	31 y-o	18 y-o	21 y-o	22 y-o	22 y-o
Type Epilepsy	GGE		Focal due to PVNH	GGE			GGE
Sz-Types	Absence, GTC		Focal w/o IOA Focal IOA	Absence, GTC			Absence, GTC, myoclonic
Time since VNS implantation	1 y, 4 m	2y, 9 m	5 y, 5 m	10 m	3y, 2 m	4 y, 4 m	3y, 2m
VNS current	3.5 mA	3.5 mA	1.5 mA	0.75 mA	2.75 mA	2.75 mA	1.75 mA
Sz-Reduction Rate	91.1%		85.7%	50.3%			35.8%
AED (mg/24 hours)	VPA 250 mg RFN 800 mg PHT 300mg	VPA 1000mg PHT 400mg	TPM 400mg LMT 400mg	CLB 30mg CLZ 1mg	CLB 20mg CLZ 2mg	CLB 25mg CLZ 1mg	LEV 3000mg PRM 750mg CLB 30mg
Gestational Age	38 w + 4 d	38 w + 1 d	40 w	37 w	39 w	38 w + 2 d	35 w + 2 d
Type Delivery	c-section	c-section	Vaginal	c-section	Vaginal	Vaginal	c-section
Reason	Failure progression	Elective, previous c-section		PE			PROM Breech presentation
Apgar (10')	9	9	dm	9	9	9	dm
Baby Weight	4420 g	3710 g	3402 g	3371 g	3373 g	3147 g	dm
Malformations	None	None	None	None	None	None	See comments*
Current Newborn Age	4 y-o	1 y-o	2 m-o	5 y-o	2 y-o	1 y-o	12 y-o

AED: antiepileptic drugs; CLB: clobazam; CLZ: clonazepam; d; days; dm: data missing; GGE: Genetic Generalized Epilepsy; GTC: Generalized Tonic Clonic; IOA: impairment of awarness; LMT: lamotrigine; m: months; m-o: month-old; PE: pre-eclampsia PHT: phenytoin; PVNH: periventricular nodular heterotopia; PRM: primidone; PROM: premature rupture of membranes; RFN: rufinamide; Sz: seizure; TPM: topiramate ; VPA: valproic Acid; w: weeks; y: years; w/o: without; y-o; year-old.

* The baby had mild dismorphic features, delay in reaching developmental milestones and a possible heart murmur, related to an interventricular aneurysm. Unfortunately, the patient was lost to follow up.

3. Results

3.1. CASE 1

The first case was a 24 year-old, right-handed woman, with drug resistant genetic generalized epilepsy (GGE)[4] manifested by daily abscences and infrequent generalized tonic-clonic seizures. The patient was treated with three different AED (see Table 1). Her brain MRI was normal and she had a positive family history of epilepsy. The first pregnancy occurred at the age of 24, over a year after the VNS implantation. She had an increase in the number of seizures during the first trimester, which improved in the following months.

There were no changes on the VNS output during pregnancy. The delivery occurred at 38 weeks via cesarean section due to a failure of labour to progress. The baby was healthy. The same patient had a second pregnancy at the age of 27, no changes in her medication regimen or the settings of the VNS were made during pregnancy. She had an elective c-section[5] at 38 weeks. There were no complications during delivery and the baby was healthy. Both babies have been developing normaly.

3.2. CASE 2

The second case was a right-handed woman with bilateral temporal periventricular nodular heterotopias and bitemporal epilepsy. She had previously tried four AED and was on two at the time of her pregnancy at the age of 31 (see Table 1). Her seizure frequency increased at the beginning of the pregnancy, afterwards she was seven weeks seizure free. During the pregnancy, no changes were made to the settings of the VNS. Vaginal delivery occurred at 40 weeks without complications.

3.3. CASE 3

The third case was a 18 year-old female who had three pregnancies after VNS implantation. She had GGE, she tried six different AED and she was taking two during the pregnancy (see Table 1). Her seizure frequency didn't change during the pregnancy and the VNS output was not changed during the gestational period. She required an urgent c-section due to pre-eclampsia at week 37 of gestation, just ten months after the VNS implantation. The baby was born without complications. The second pregnancy occurred three years after the VNS implantation, without any changes in medication or VNS parameters. It resulted in a healthy baby, born via vaginal delivery at 39 weeks without any complications. The third pregnancy occurred at the age of 22, over four years since the VNS implantation. She had a vaginal delivery at 38 weeks without complications resulting in a healthy baby.

3.4. CASE 4

The fourth case was a 22 year-old female, with a history of GGE, mild intellectual disability (ID)[6] and tried eight different AED (see Table 1). The pregnancy happened more than three years after the VNS implantation and she was taking three AED. She had one generalized tonic-clonic seizures every two to three months during the pregnancy. The VNS was turned off at 26 weeks of pregnancy, due to concerns of a possible teratogenicity. However, due to an increase in seizure frequency, the VNS was turned on a month later. She had a c-section, due to spontaneous rupture of the amniotic sac and breech presentation. At the last follow up there were some concerns regarding mild dismorphic features of the baby and a possible heart murmur, related to aninterventricular aneurysm. Unfortunately, the patient was lost to follow up. No further information could be obtained.

[4] GGE: Genetic generalized epilepsy.
[5] c-section: caesarean section.
[6] ID: Intellectual disabilities.

Table 2
Summary of the publications reporting the use of VNS in pregnancy [4−11].

Study	N Woman	Epilepsy Type	N Pregnancies	Age at time pregnancy	Average current	Type Delivery	Maternal Complications	Malformation	Maternal, fetus or baby death
(Ben-Menachem et al., 1999)	2	Dm	2	Dm	Dm	Dm	None	None	None
(Kalayjian and Heck, 2005)	2	Focal	3	38	0.5 mA	Dm	None	None	None
(Houser et al., 2010)	1	Generalized	1	19	Dm	Vaginal	1 PE	None	None
(Galbarriatu et al., 2015)	1	Focal	1	Dm	Dm	Dm	None	None	None
(Salerno et al., 2016)	1	Focal	1	27 y-o	2 mA	c-section	None	None	None
(Rodríguez-Osorio et al., 2017)	4	4 Focal	5	31.8 y-o	1.25 mA	2 c-section 2 vaginal	1 PROM 1 Rh Incompatibility	None	1 miscarriage (1 st T)
(Sabers et al., 2017)	25	17 Focal 3 GGE 5 Unclassified	26	31 y-o	1.6-1.8 mA	10 vaginal 10 c-section 2 vacuum extraction 2 induced labors	None	1 major malformation	1 miscarriage (8 w-p)
(Husain et al., 2005)	1	Depression	1	28	0.25 mA	Vaginal	None	None	None
Suller et al (present study, 2019)	4	3 GGE 1 Focal	7	22 y-o	1.75 mA	4 c-section 3 vaginal	1 PE 1 PROM & BP 1 FTP	1 major malformation	None

Avg: Average; BP: breech presentation; Dm: data missing; GGE: Genetic Generalized Epilepsy; FTP: failure to progress; PE: pre-eclampsia; PROM: premature rupture of membranes; T: trimester; w-p: weeks of pregnancy.

4. Discussion

We presented four patients with DRE who underwent VNS implantation prior to pregnancy. There were seven pregnancies resulting in six healthy babies. One of the seven babies had an intellectual disability and a cardiac malformation. Even though this could have been related to VNS, there were other risk factors including high doses of AED and a potential genetic influence. In all cases, birth weight, Apgar scores and duration of pregnancy were normal.

VNS is used in all ages, including potential childbearing population. There are concerns that VNS can increase the risk of obstetric complications during the pregnancy and at the time of the delivery, as well as possible teratogenic effects to the newborn. The information in that regard is limited even though it is a device commonly used to treat epilepsy. There are only 35 cases published worldwide investigating the outcome of those with epilepsy on treatment with VNS during pregnancy (Table 2 summarizes the cases reported in the literature) (Sabers et al., 2017; Rodríguez-Osorio et al., 2017; Ben-Menachem et al., 1999; Galbarriatu et al., 2015; Houser et al., 2010; Kalayjian and Heck, 2005; Salerno et al., 2016; Husain et al., 2005).

Another important outcome is the type of the delivery and obstetric complications. Several studies of pregnant woman who have epilepsy have shown that this population has increased risk of obstetric complications (Mawer and Liverpool and Manchester Neurodevelopment Group, 2010; The North American Pregnancy and Epilepsy Registry, 2005; Kelly et al., 2013). In our series there were three obstetric complications over seven deliveries, requiring four c-sections, and only one was elective. Therefore, c-section was necessary in 57% of the pregnancies observed in this series. This number is higher in comparation to the Canadian rate of 26.9% (Komisaruk et al., 2004). The pathophysiology of the obstetric complications may be related to the uterine input received from the vagus nerve, which behaves as a bidirectional bridge between the central nervous system and uterus (Judkins et al., 2018).

The refractory nature of the patients' epilepsy included in this series is something to consider as the refractory nature of their epilepsy was the reason for VNS implantation. All patients were taking several AED during their pregnancy. Polytherapy has shown to increase the risk of fetal malformation (Mawer and Liverpool and Manchester Neurodevelopment Group, 2010). VNS can reduce seizure frequency, and might mitigate teratogenic risk if the number or doses of AED can be reduced.

The VNS has also been approved in some countries for refractary depressive cases, but there is less published on VNS and refractory depressive patients compared to epilepsy. One case published investigated a depressive pregnant women who became pregnant while she was using the device and had an uneventful delivery with a full term healthy baby (Husain et al., 2005).

Experimental epilepsy models using rats and rabbits receiving VNS stimulation during pregnancy, found no adverse effect on either the pregnancy or on neonatal viability (Danielsson and Lister, 2009). In a similar study with rabbits, the fetuses did not show any skeletal and soft tissue abnormalities (O'Keane et al., 2005). Both studies used a similar output current of stimulation, but the durations of the stimulation were different. It is not clear if the total time during which the fetus was exposed to the stimulation can impact the outcome. Another important finding in a different study found that VNS does not affect the level of pittuitary hormons (LH, FSH, prolactin)[7] .

Other implatable devices which have been used more frequently, such as cardiac pacemakers, do not cause any limitations during pregnancy (Auricchio et al., 2013). In the case of Deep Brain Stimulation (DBS)[8], a small case series, including eleven pregnant women

[7] LH: Luteinizing hormone; FSH: Follicle-stimulating hormone

[8] DBS: Deep Brain Stimulation

implanted with DBS, found no side effects or complications for the mother or the baby (Scelzo et al., 2015).

This study has several important limitations. The small size of the sample, the retrospective character and the lack of neurocognitive evaluation of the newborns are the most significant.

5. Conclusions

Given the limitations of the study, it can be only hypothesized, that VNS is a well tolerated therapy and may reduce polypharmacy during pregnancy. However, the obstetrical complications may be higher than in patients without VNS, with low risk of congenital malformations. A prospective multicentre study is needed to accurately determine safety and potential teratogenicity of VNS.

Ethical publication

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

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