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Pregnancy and deep brain stimulation therapy for epilepsy

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ABSTRACT

Objective. Neuromodulation therapy -vagus nerve stimulation (VNS) and deep brain stimulation (DBS)- is one of the therapeutic options for drug-resistant epilepsy. With the increasing number of DBS implantations in women with epilepsy, it has become a burning issue whether DBS is safe in pregnancy. We report here two women with epilepsy who gave birth to healthy children with DBS therapy.

Methods. We describe two cases, a 30-year-old woman and a 37-year-old woman. Both were implanted with DBS due to drug-resistant epilepsy.

Results. Both of our patients showed a significant improvement after DBS implantation and thereafter gave birth to a healthy child with DBS treatment. The severity and frequency of epileptic seizures did not change during pregnancy and after childbirth. Although a Caesarean section was performed in one case, pregnancies and births were essentially problem-free. At present, the two- and four-year-old children are healthy.

Significance. Considering these cases, previously described VNS cases, and DBS cases with non-epileptic indications; we suggest that pregnancy and childbirth are safe in epilepsy patients with DBS, moreover, DBS treatment has probably no effect on foetal abnormalities or breastfeeding.

Key words: deep brain stimulation; epilepsy; women of childbearing age; pregnancy; risk; foetal malformations; maternal mortality

Neuromodulation therapy-primarily vagus nerve stimulation (VNS) and deep brain stimulation (DBS)- is one of the therapeutic options for drug-resistant epilepsy. A double-blind randomized trial demonstrated the long-term efficacy and safety of ANT-DBS (DBS of the anterior nucleus of thalamus) [1]. Thus, ANT-DBS has become the most commonly used DBS approach for epilepsy, especially after its approval in Europe in 2010 and in the United States in 2018.

With the increasing number of DBS implantations in women, it has become a burning issue whether ANT-DBS is safe in pregnancy, especially because maternal mortality and incidence of foetal malformations are higher in pregnant women with epilepsy [2, 3]. It seems particularly problematic that some long-term post-marketing DBS trials in epilepsy virtually exclude women of childbearing potential who want a child in the long run, without any evidence on the adverse effects of DBS treatment on pregnancy (for example: ClinicalTrials.gov #NCT03900468, or #NCT04164056). DBS treatment, as opposed to antiseizure drugs, cannot be stopped easily; when starting DBS treatment, it should be borne in mind that the majority of young women may want a child sooner or later. Because we have not found any published studies addressing this issue, we decided to report our experience of two women with epilepsy who gave birth to healthy children with DBS therapy.

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Methods

Eleven patients with focal drug-resistant epilepsy were treated with ANT-DBS at our centre between 2011 and 2020. Implantations were performed after a presurgical evaluation that included high-resolution MRI and ictal video-EEG recordings [4].

DBS implantation protocol

All subjects were scanned on a 1.5T MRI scanner (MAGNETOM Avanto fit, Siemens Healthcare, Erlangen, Germany) with a 20-channel Head/Neck coil. A T1-weighted 3D MPRAGE sequence was utilized. For surgical planning, T1WI 1-mm thin slices with contrast and axial T2WI MRI sequences were obtained for multiplanar reconstruction, in all three orientations. Surgical planning was performed using Medtronic Framelink 5 Stealth Station software. The preliminary empirical surgical target was at 5-6 mm lateral, 12 mm superior and 0-2 mm anterior to the midcommissural point (MCP). The target was then individually adjusted according to individual anatomy using the mamillothalamic (mtt) tract as a landmark. The trajectory was planned to run primarily transventricularly avoiding major visible vascular structures on contrast-enhanced T1 images. Surgery was performed under general anaesthesia, using the CRW Precision™Arc System. DBS electrodes were implanted via insertion cannula, extending 10 mm above the planned target under control of intra-operative fluoroscopy and fixed to the skull.
Postoperative care and device programming were in accordance with the guidelines of the SANTE study [1].
Two of our DBS patients had pregnancies and gave their written consent to the disclosure of their cases. Retrospective case reports do not require ethical committee approval.

Patient 1 (see *table 1* for more details)

This 30-year-old woman had epilepsy since age 14. Her seizures were initiated by an aura (characterized by a strange feeling in her throat), followed by focal-onset impaired-awareness seizures (FOIA; according to previous classifications: psychomotor seizure), accompanied by automatisms. These seizures occurred 1-6 times a day. Once a year, focal-to-bilateral tonic-clonic seizures (FBTC; according to previous classifications: grand mal seizures) emerged.
At age 23, the patient underwent a presurgical evaluation at our centre due to drug resistance. Long-term video-EEG showed right temporal interictal epileptiform discharges, and during all seven video-EEG-captured FOIA seizures, a right temporal seizure pattern was seen. 3-Tesla brain MRI with a specific epilepsy protocol revealed right-sided fronto-temporal abnormalities. The neuropsychological evaluation showed impaired verbal fluency and disturbance in non-verbal (visual) working memory. Functional MRI showed left-sided speech centres. In 2013, the patient underwent a right fronto-temporal extended lesionectomy. Histology showed ganglioglioma (WHO Grade 1).
Because her seizures continued to occur postoperatively, we decided to introduce DBS therapy in 2014. The 3387 (40 cm) type leads (Medtronic, Minneapolis, MN, USA.) were transventricularly implanted into the antero-principalis thalamic nuclei using stereotaxic navigation. Then, an Activa PC-type (Medtronic, Minneapolis, MN, USA) pulse generator was implanted in the left subclavicular region under the pectoral muscle. One month after surgery, we turned on the ANT-DBS (3 V, 90 µs, 140 Hz). Between 2014 and 2015, we gradually increased the stimulation voltage to 5.5 V. A significant decrease in seizure number was observed; FOIA seizures occurred 5-8 times per month, while FBTC seizures no longer occurred.
Although the patient cooperated well and was regularly controlled, in early 2016, when she applied to our outpatient clinic, she was found to be 20 weeks pregnant. The pregnancy was not planned. At this time, she was taking valproate (2,000 mg/day), levetiracetam (2,000 mg/day), lacosamide (300 mg/day), carbamazepine (1,200 mg/day), and folic acid (1 mg/day). Drug levels were shown to be: carbamazepine at 6.5 mg/L and valproate at 54 mg/L. Although we were aware that this medication regime poses a high risk of foetal abnormalities, we decided not to initiate a significant change in medication. In agreement with the patient, the dose of valproate was reduced by only 500 mg, while the dosage of the other medications remained unchanged. This decision was based on the following considerations:

- the pregnancy was relatively advanced, so we were no longer able to reduce the risk of developing major congenital malformations through drug switching;
- and with current DBS settings and drug therapy, seizures became infrequent, while FBTC seizures completely resolved, implying a better quality of life and a lower risk of sudden unexpected death in epilepsy (FBTC seizures may be responsible for the higher mortality of pregnant women with epilepsy) [5, 6].

High-resolution foetal ultrasound (at 18 and 31 weeks of gestation) showed no abnormalities.
Due to a non-reactive non-stress test and threatening asphyxia, a Caesarean section was performed under general anaesthesia at 40 weeks of gestation. During

▼ **Table 1.** Detailed description and comparison of our two patients who became pregnant with DBS therapy.

	Patient 1	Patient 2
Age (years)	30	38
Age at epilepsy onset (years)	14	13
Resistant to the following antiseizure drugs	zonisamide, topiramate, lamotrigine, oxcarbazepine, levetiracetam, valproate, lacosamide, carbamazepine	valproate, oxcarbazepine, clonazepam, levetiracetam, phenytoin, gabapentin
Neuroimaging, histology	MRI: right fronto-temporal lesion, histology: ganglioma WHO I.	MRI: normal, SPECT: right occipital hypoperfusion
Interictal epileptiform discharges on EEG	right temporal	right fronto-central
Seizure pattern on EEG	right temporal	bilateral
Presurgical evaluation and resective surgery	right frontotemporal resection: failed	not eligible for resective surgery
DBS implantation	2014	2011
Seizures before DBS implantation	Aura+FOIA: 1-6/day FBCS: 1/year	Aura+FOIA: 1/day FBCS: 3-4/year
Seizures after DBS implantation	Aura+FOIA: 5-8/month FBCS: none	Free of disabling seizures
Age at pregnancy (years)	26	36
Antiseizure medication during pregnancy	levetiracetam, valproate, lacosamide, carbamazepine	lacosamide, zonisamide, clobazam
DBS parameters during pregnancy	5.5 V, 90 µs, 140 Hz ON: 1 min, off: 5 min	6.5 V, 90 µs, 140 Hz ON: 1 min, off: 5 min
Type of delivery	Caesarean section due to no-reactive non-stress test without major complications	spontaneous delivery without complications
Gestational age at childbirth	40. week	35.week
Newborn: weight / length / head circumference	3650g/55cm/34cm	2900g/49cm/33cm
Apgar score (at 1 minute and 5 minutes after birth)	9/1 and 10/1	9/1 and 10/1
Follow-up after childbirth	4 years, 2 months	2 years, 7 months
Newborn: malformation or psychomotor delay	No	No
Breast-feeding	2 weeks	No
Other potential obstetric complications	-	surgery due to ectopic pregnancy 1 year before delivery

DBS: deep brain stimulation; FOIA: focal-onset seizures with impaired awareness; FBCS: focal-to-bilateral tonic-clonic seizures; MRI: magnetic resonance imaging; SPECT: single photon-emission computer tomography; WHO: World Health Organization.

surgery, the DBS was turned off and only bipolar cautery was used. Postoperatively, the DBS was turned on to its original parameters. There were no postoperative complications or seizures around childbirth. Breastfeeding was completely stopped after a few weeks because there was not enough breast milk. The frequency and severity of seizures did not change during pregnancy and the postpartum period.

The child was born with a weight of 3,650 g and an Apgar score of 9/1-10/5. In 2020, the child is now four years old. He is healthy and his psychomotor development is normal.

Patient 2 (see *table 1* for more details)

This 37-year-old woman had drug-resistant epilepsy since age 13. The patient had FOIA seizures accompanied by manual automatisms (on average, one per day). In addition, three to four FBCS seizures per year also occurred. These seizures were most often initiated by an aura that the patient could not describe in detail.

High-resolution brain MRI with a specific epilepsy protocol was normal. During video-EEG monitoring, we captured four FOIA seizures, of which two propagated into FBCS seizures. During the seizures, a bilateral fronto-lateral EEG seizure pattern was seen. Interictal EEG showed right-sided fronto-central sharp waves. A detailed and repeat neuropsychological examination found no cognitive deficit. Based on these findings, the presurgical team decided not to recommend resective surgery for the patient due to poor surgical prognosis [7].

In May 2011, bilateral DBS electrode implantation was performed into the anterior thalamus nuclei. Repeat surgery was performed in November 2011 because the electrode was misaligned based on postoperative MRI. Thereafter, the DBS was switched on and stimulation parameters were gradually increased (6.5 V, 90 µs, 140 Hz).

With this DBS setup, FBCS seizures last appeared in 2014. In addition to further increasing stimulation parameters and parallel antiseizure drug adjustment, FOIA seizures also ceased; with the help of the patient programmer, the patient could stop the seizures in the aura phase. In October 2016, a generator was replaced due to battery depletion. In the spring of 2017, surgery was performed for ectopic pregnancy.

The patient planned to become pregnant during 2017, therefore folic acid, at 3 mg daily, was recommended, but as the patient did not have disabling seizures with the set DBS parameters and antiseizure drugs (lacosamide at 450 mg/day, zonisamide at 500 mg/day, and clobazam at 10 mg/day), we did not change the therapeutic setting.

In March 2018, in the 35th week of pregnancy, spontaneous delivery took place. Epidural anaesthesia was used. The child was born with a weight of 2,900 g, length of 49 cm, head circumference of 33 cm, and Apgar score of 9 / 1-10 / 5. Breastfeeding was suspended in the postpartum period after informing the patient about the benefits and risks of breastfeeding with concomitant antiseizure drugs. In November 2020, the currently 31-month-old child is healthy and her psychomotor development is normal. The frequency of seizures remained unchanged during pregnancy and after delivery. The patient is currently free of disabling seizures and planning to have another child.

Discussion

Both of our patients showed a significant improvement after DBS implantation and thereafter gave birth to a healthy child on DBS treatment. The severity and frequency of epileptic seizures did not change during pregnancy and after childbirth. Although a Caesarean section was performed in one case, pregnancies and births were essentially problem-free. It is important to note that almost half of pregnancies in Hungary result in Caesarean section [9].

Data are available for another neuromodulation therapy in pregnant women with epilepsy, that of VNS. Suller Marti and colleagues investigated four cases of their own and an additional 37 published female patients, making a total of 47 pregnancies in 41 patients with epilepsy treated with VNS (five patients were pregnant several times) [9]. The authors reported two major malformations (4%) and two miscarriages (4%) in this cohort. Caesarean sections were performed in half of the cases. Based on this relatively small number of cases, the authors hypothesized that:

- VNS may slightly increase the chances of birth complications, although the effect of concomitant drug therapy was not excluded;
- foetal harm due to VNS is unlikely [9].

Several pregnancies have been reported during treatment with DBS in patients with non-epileptic indications.

Scelzo *et al*. reported the pregnancies of 11 patients with DBS implantation due to Parkinson's disease, dystonia, Tourette's syndrome, and obsessive-compulsive disorder [10]. With the exception of a miscarriage of a foetus from a twin pregnancy, foetal development was undisturbed during all pregnancies, and healthy children were born [10].

The pregnancies of patients with generalized dystonia treated with DBS are reported in four studies; a total of 10 pregnancy cases were reported [11-14]. These studies reached similar conclusions: pregnancy is safe, there is no evidence that DBS is harmful to the foetus, and DBS does not pose a problem for childbirth or breastfeeding [11-14].

Considering our own cases, previously described VNS cases, and DBS cases in patients with non-epileptic indications, we suggest that epilepsy patients with DBS may have a safe pregnancy and childbirth, and DBS treatment has probably no effect on foetal abnormalities or breastfeeding. Therefore, in long-term neuromodulation studies and registries, the criterion to exclude pregnant women could be unnecessary, as otherwise young and healthy epileptic women are excluded. The main limitation of our study is that the data are based on case reports only; a multicentre study is therefore necessary to show the safety of neuromodulation devices in pregnant women and women with childbearing potential. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) Which of the following are not recommended therapeutical options for women with epilepsy and childbearing potential:
A. carbamazepine + deep brain stimulation
B. resective surgery + folic acid + levetiracetam
C. vagus nerve stimulation + lacosamide
D. ketogenic diet + folic acid + valproic acid

(2) The patient is unlikely to be seizure-free after:
A. introduction of an antiseizure drug after a first unprovoked seizure
B. temporal lobectomy for mesial temporal lobe epilepsy
C. introduction of neuromodulation therapy
D. status epilepticus due to non-compliance

(3) The risk of SUDEP may be higher:

A. if focal-to-bilateral tonic-clonic seizures are present
B. when switching from valproate to lamotrigine at 30 weeks of gestation
C. in Dravet syndrome
D. in all of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".