■ Case vignette

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Deep brain stimulation (DBS) of anterior nucleus thalami (ANT) in female epilepsy patients during pregnancy and delivery: experience from two cases

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For patients with drug-refractory epilepsy, deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) can be a therapeutic option [1-4]. During pregnancy, continuation of DBS cannot generally be recommended as there is insufficient data to justify this. There are 20 reported cases of pregnancy without complications under continued DBS of the subthalamic nucleus, globus pallidus internus, and thalamic ventral intermedius nucleus [5-7], but no cases under cyclic ANT-DBS. We report two female epilepsy patients with ANT-DBS during pregnancy, delivery, and the postpartum period.

Patient A, a 28-year-old, and Patient B, a 27-year-old, were in good health with normal neurological status and had a history of frontal lobe epilepsy since the age of three and 11, respectively. Both had hyperkinetic seizures mostly during sleep. Patient B also had focal to bilateral tonic-clonic seizures. Aetiologies were unknown; in Patient A, 3T MRI was normal including morphometric analysis, CSF, and positron emission tomography (PET). Ictal EEGs showed focal frontal rhythmic activity. The epilepsies of the patients became drug-refractory. Last established antiseizure medications (ASM) were lamotrigine/levetiracetam (Patient A) and oxcarbazepine (Patient B). Patient A had 4-5 seizures a week, up to 4-5 times a night, and Patient B 5-20 hyperkinetic seizures per week and one focal to bilateral tonic-clonic seizure per year.

Table 1 provides a summary of both patients' presurgical work-up. For the possible resections in these patients, Phase 2 evaluation would have been necessary, however, both patients declined. Instead, they favoured neurostimulation and decided on ANT-DBS because of possible vocal impairment associated with vagus nerve stimulation (VNS).

Both patients underwent bilateral implantation of DBS electrodes (model 3389; Medtronic, Minneapolis, Minnesota, USA) into ANT at the Neurosurgical Department of the University Hospital Hamburg-Eppendorf, Germany. Since an extraventricular approach was used, DBS electrodes with reduced space (model 3389, Medtronic) were chosen ('off-label' use) to achieve the best coverage of ANT and the mammillothalamic tract [8]. Pulse generators (Activa PC; Medtronic) were implanted in the pectoral region.

DBS activations (one and two months later) and programming were performed at the Hamburg Epilepsy Center (which has experience of ANT-DBS in 30 epilepsy patients since 2011). Stimulation parameter frequency (145 Hz),

▼ **Table 1.** Summary of both patients' presurgical work-up.

Presurgical work-up	Patient A	Patient B
Age (years)	28	27
Neurological status	Normal	Normal
Age at onset of epilepsy (years)	3	11
Type of epilepsy	Frontal lobe epilepsy	Frontal lobe epilepsy
Seizure type	Hyperkinetic seizures (only during sleep)	Hyperkinetic seizures +bilateral tonic-clonic seizures (during sleep > while awake)
Seizure frequency	4-5 seizures a week up to 4-5 times a night	5-20 hyperkinetic seizures per week + 1 focal to bilateral tonic-clonic seizure per year
Interictal EEG	Bifrontopolar focus without lateralization (Fp1 > F3, C3 + Fp2 > F4,C4)	2 foci: left fronto-central (F3, Fz, C3, Cz > Fp1) + left temporal anterior (F7, T1, T3)
Ictal EEG	Bifrontopolar rhythmic activity without lateralization (Fp1 + Fp2)	Left fronto-central (F3, Fz, C3, Cz) rhythmic activity often with left temporal propagation
Antiseizure medication (ASM)	Carbamazepine, oxcarbazepine, levetiracetam, lamotrigine, lacosamide, zonisamide, pregabalin	Phenytoin, lamotrigine, zonisamide, clobazam, levetiracetam, oxcarbazepine
Last established ASM	Lamotrigine/levetiracetam	Oxcarbazepine
High-resolution 3T MRI	Normal	Normal
MRI postprocessing (morphometric analysis)	Normal	Normal
CSF including antineuronal autoantibodies	Normal	Normal
Positron emission tomography (FDG-PET)	Normal	N/a
Ictal SPECT	N/a	Regional left frontal hyperperfusion
Language lateralization (fTCD)	N/a	Left
Phase 2 evaluation	Necessary, but declined	Necessary, but declined

pulse width (90 µsec), on time (1 min), and off time (5 min) were equal in both patients. Although the therapeutic current accounts for the antiepileptic effect, we describe the DBS stimulation in the following based on stimulation amplitude measured in Volts.

In Patient A, cathode contacts 2/9 were stimulated up to 5 V. Due to inefficiency, unipolar stimulation was intensified by adding cathode contacts 3/10. At up to 4 V, seizure frequency could be decreased by 75% within four months. As sleep quality decreased with further increases in amplitude stimulation, "bilevel" stimulation (4 V at night, 5 V during the day) was established [9], followed by determining the best times for day/night switching to obtain optimal tolerability. Seizure frequency was finally reduced by 85% without sleep disturbances.

After DBS activation in Patient B (initially cathode contacts 1/9 and cathode contacts 2/10 added later on), amplitude stimulation with 2 V resulted clinically in memory and concentration problems and emotional instability, disappearing immediately after reduction to 1.5 V. One month later, the same side effects reappeared with 2.5 V and again disappeared under 2 V. With only one hyperkinetic seizure per month over the next five months, the DBS therapy effect was promising. Further attempts to raise the voltage repeatedly failed.

Ten months (Patient A) and two weeks (Patient B) after DBS activation, contraception was discontinued, and two months and four months later, the patients became pregnant for the first time. As explicitly requested, ANT-DBS was continued and ASM were adapted to three daily intakes and elevated during pregnancy.

In Patient A, seizure frequency remained stable. In Patient B, initially more focal seizures occurred. Oxcarbazepine serum levels dropped to 50-60% of the pre-pregnancy values (24-26 mg/L), rising again under increased oxcarbazepine dosages. Subsequent DBS optimization at 2.5 V was now tolerated. Except for one bilateral tonic-clonic seizure shortly before delivery, no further pregnancy complications occurred. Seizure control was down to one focal seizure every 2-3 months.

After nine months, both patients gave birth via Caesarean sections as the desired birth modus, which were performed following the DBS manufacturer's safety recommendations, *e.g.*, pausing DBS stimulation and avoiding monopolar coagulation. To date, both children are healthy, based on regular check-ups (*table 2*). Patient A, being sufficiently content, did not want any further DBS changes, and to date, seizure frequency has remained stable. For Patient B, due to the presence of seizures, amplitude stimulation was gradually increased to 2.9 V and oxcarbazepine was elevated. To date, three focal seizures per month have occurred.

Although DBS continuation during pregnancy cannot generally be recommended due to insufficient data at the present time, there are 22 documented pregnancies without complications: 20 cases under non-ANT and our two cases under ANT-DBS presented here.

There are no known potential ANT or non-ANT DBS-related risks for pregnancy or fertility.

However, as for ANT-DBS, pulsatile stimulation of the ANT may theoretically result in potential problems regarding fertility and pregnancy because both depend on complex hormonal changes in the hypothalamic-pituitary-ovarian axis, and the mamillary bodies of the hypothalamus are part of the Papez circuit stimulated by ANT-DBS. An example of such a potential network disturbance evoked by ANT-DBS is

▼ **Table 2.** Delivery and follow-up of the patients' children.

Delivery + first check-up (U1) (2^{nd} – 4^{th} hour)	Patient A's baby boy	Patient B's baby girl
Age (week of gestation)	37+5	36+6
Birth modus	Primary Caesarean section	Primary Caesarean section
Foetal position	Cephalic presentation	Cephalic presentation
Umbilical pH	7.34	7.32
APGAR	7/8/9	9/10/10
Length (cm)	57	49
Head circumference (cm)	37	35
Weight (g)	3745	2790
Birth complication/trauma/abnormality	Respiratory adaptation disorder (temporary CPAP therapy)	Small patent foramen ovale
Malformation	No	No
Pulse oximetry screening	100%	99%
Vitamin K prophylaxis	Yes (2 mg)	Yes (2 mg)
Following check-ups		
3^{rd} – 10^{th} day (U2)	Normal	Normal
4^{th} – 5^{th} week (U3)	Normal	Normal
3^{rd} – 4^{th} month (U4)	Normal	Normal
6^{th} – 7^{th} month (U5)	Normal (convergent strabismus)	Normal
10^{th} – 12^{th} month (U6)	Normal	N/a
21^{st} – 24^{th} month (U7)	Normal	N/a

ANT-DBS-induced sleep disruption via co-stimulation of the anatomically nearby ascending reticular activating system (ARAS) [9].

ANT-DBS in fact did not prevent our two patients from becoming pregnant after only a few monthly cycles following discontinuation of contraception. Moreover, besides the continuation of ANT-DBS itself, increases in amplitude stimulation made during Patient B's pregnancy appeared to have no negative consequences.

We present the first two pregnancies under ANT-DBS with documentation before conception and up to six and 24 months after delivery, respectively. No complications occurred. Clearly, more evidence is needed for a general recommendation of ANT-DBS continuation under pregnancy which is indicated by this case vignette. However, the information provided may be useful for ANT-DBS counselling and handling of female epilepsy patients who want, or potentially want to have children, as well as during pregnancy and delivery. ■

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

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TEST YOURSELF

(1) Are there reported cases of pregnancy under continued DBS therapy?

(2) Can ANT-DBS continuation be recommended during pregnancy?

(3) Does ANT-DBS therapy prevent female patients from becoming pregnant?

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