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Short Communication

Unmet Need in Early-Onset Parkinson's Disease: Deep Brain Stimulation and Pregnancy

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Abstract. Pregnancy in women with early-onset Parkinson's disease (PD) is likely to have a higher frequency given the trend toward increasing maternal age, thus resulting in a greater overlap time between childbearing age and PD risk. Deep brain stimulation (DBS) therapy is nowadays offered to PD patients at earlier stage of the disease, when women can still be pre-menopausal. However, few data are available about DBS safety during pregnancy. From a review of the available literature, only one article was published on this topic so far. Therefore, we have developed a clinical consensus on the safety of DBS during pregnancy in PD patients.

Keywords: Parkinson's disease, deep brain stimulation, pregnancy

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INTRODUCTION

More than 300,000 patients worldwide have received deep brain stimulation (DBS) therapy for movement disorders, mainly for Parkinson's disease (PD) [1].

According to newly proposed guidelines on invasive therapies in PD, DBS of the subthalamic nucleus (STN) and the globus pallidus internus (GPi) can be recommended in early stages of PD, when fluctuations are already present, or in medically unresponsive tremor-dominant PD [2, 3]. Recommendation to DBS is even more relevant in the setting of juvenile onset PD and early-onset PD (EOPD), for which the newly proposed age-cut off is 21 to 50 years [4]. EOPD represents 3 to 7% of all PD cases with incidence of 0.29–3.3 per 100,000 person-years depending on the age cut-off [5–8]. Approximately 400 women under the age of 50 are diagnosed with PD annually in the United States alone [9]. Whereas the incidence of pregnancy in women with PD is unknown, we hypothesize that it is rising given overlapping epidemiologic trends in both PD risk and increasing maternal age [10, 11]. Therefore, it is crucial to customize PD treatment to accommodate life choices, encompassing both personal and professional aspects. Furthermore, it's imperative to recognize sex and gender differences, particularly regarding issues like pregnancy. Data regarding the safety of dopaminergic treatment during pregnancy are limited [11]. STN DBS, by offering the possibility to discontinue medication, could be a viable option for PD women desiring pregnancy. Conversely, women with PD might be undertreated, with lower rates of DBS utilization compared to men [12]. This disparity could hinder their family planning due to the severity of parkinsonian symptoms and inadequate symptom control. However, the safety of pregnancy in the context of DBS remains uncertain.

Therefore, we aimed to review the available data on DBS and pregnancy in PD, to summarize the available evidence and experience, and make recommendations.

METHODS

We performed a systematic review of the available literature in PubMed from database inception through September 2023, with the following search terms: deep brain stimulation OR DBS AND pregnancy AND Parkinson's disease. The inclusion criterion was an original research article on DBS co-occurring with pregnancy. Exclusion criteria were (1) duplicate publications, (2) reviews or non-research articles, (3) articles that did not include information about pregnancy, (4) articles not in English.

RESULTS

From 45 articles found our review included only one, reporting three PD patients and three pregnancies, all with biallelic PARK-PRKN variants [13]. We reached out to the article's authors to obtain previously unpublished data (Table 1). All patients had bilateral STN DBS with neurostimulators implanted in the right subclavicular region before becoming pregnant. No adverse effects during pregnancy were reported. Delivery was described only in one patient and occurred at full term by caesarean section (c-section) because of the baby's abnormal position. It was performed under general anesthesia, with DBS turned off, and with bipolar cautery. Two patients did not breastfeed their babies due to the unknown toxicity of dopaminergic therapy in breast milk. DBS settings were not adjusted during pregnancy. Patient 1 and 3 (in Table 1) discontinued oral dopaminergic medications during pregnancy. However, Patient 3 reintroduced oral therapy during the 6th month of pregnancy due to mild worsening of the motor fluctuations (Table 1) without any apparent impact on pregnancy and baby's health. Motors scores improved during pregnancy in Patient 1, with return to pre-pregnancy scores about 20 days after delivery. After delivery, Patient 1 experienced an occasional worsening of her right leg dystonia and impairment in walking, but her motor score remained unchanged. The patient remained independent and was able to take care of her baby. In another patient (Patient 2), motor scores remained stable during pregnancy and 14 months after delivery [13].

DISCUSSION

Our review demonstrates the paucity of evidence for the safety of DBS in pregnant women with PD, emphasizing the need for proactive solutions. Considering the challenges faced by juvenile and EOPD patients in making life-altering decisions, especially during pregnancy when medication may pose risks, exploring alternatives like DBS becomes crucial [2]. Scelzo et al. reported three PD patients with juvenile onset PD and pathogenic variants in the *PRKN* gene.

Table 1
Characteristics of the included patients

Patients	Age at onset	Age at DBS	Age at delivery	Indication for DBS	DBS Target	MDS-UPDRS part III score		Medication		LEDD pre DBS	LEDD Post DBS	MDS UPDRS part III scores (STIM ON/MED ON)			
						Before DBS (MED ON)	1 year after DBS (MED ON STIM ON)	Before DBS	After DBS			Before pregnancy	During pregnancy	After pregnancy	Last follow-up
Patient no 1	19	35	37	Severe "off" painful dystonia, dyskinesia, and dopamine dysregulation syndrome	Bilateral STN	19	9	Levodopa/carbidopa: entacapone 350 mg/day, pramipexole 0.9 mg/day	Pramipexole 1,05 LP, Rasagiline 1 mg	545	105	26 (one month before)	8 (at 4 months)	27 (20 days after delivery)	29 (23 month after the delivery)
Patient no 2	14	30	33	Severe dyskinesia, wearing off, early morning akinesia; and hyperdopaminergic behavior	Bilateral STN	5	11	Levodoa/benserazide 300 mg/day; ropinirole 6 mg/day	Piribedil 300 mg/day	400	500	11 (17 months before)	11 (at 5 months)	11 (14 months after delivery)	22 (42 months after the delivery)
Patient no 3	18	39	43	Severe dyskinesia, painful off dystonia, tremor in the left side, and hyperdopaminergic behavior	Bilateral STN	30	8	Levodopa/benserazide 600 mg/day; ropinirole LP 8 mg/day	Bromocriptine 15 mg/day; levodopa/carbidopa LP 200 mg/day	733	300	**NA**	**NA**	NA	NA

LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society-Unified Parkinson Disease Rating Scale.

This is the most common cause of autosomal recessive PD, accounting for between 2.6% and 14.9% of cases of juvenile and EOPD. The typical presentation of *PRKN*-PD is characterized by an early age at onset, a pure motor disease with an excellent response to dopaminergic therapy, slow progression, and a lack of cognitive decline [14]. However, one of the reported patients developed severe behavioral disorders while on oral dopaminergic drugs, resulting in marital breakdown, loss of child custody, depression, suicidal ideation, and social isolation [13]. After bilateral STN DBS surgery, motor symptoms improved, and therefore, dopaminergic therapy was reduced with clear improvement of her behavioral symptoms. The patient not only regained custody of her children but also decided to have another baby. At follow up, she was fully independent and able to care for all her children [13, 15].

Approximately 65% of women with PD experience worsening of their symptoms during pregnancy due to various physiological changes [9, 11]. Potential advantages of STN DBS include creating a more secure space to consider pregnancy through a better symptom control and permitting a reduction in pharmacotherapy, thus limiting fetal exposure to oral agents. Indeed, the evidence on the safety of dopaminergic therapy in pregnancy remains limited, although spontaneous abortion does not seem more frequent after exposure to levodopa compared with the general population [11, 16].

Currently, there are no available guidelines on the management of PD during pregnancy, and certainly not on PD women with DBS and pregnancy. With multidisciplinary teams being created to support holistic treatment of PD, this model should be incorporated to establish obstetric best medical practice in pregnant patients. Based on a survey of 15 obstetricians, the following proposal was suggested for women with PD: 1) normal schedule of prenatal appointments, 2) prenatal counselling with a neurologist, and 3) method of delivery chosen based on standard obstetric indications [17]. Additionally, neurological review within 24 hours of delivery and obstetric high-dependency monitoring were suggested [11, 17]. Moreover, addressing the uncertainty among pregnant PD patients about disease progression and DBS management is essential for patients safety [18]. Ideas for management include having neurologists provide information on the DBS device to the obstetric and anesthetic team at an early stage of pregnancy. Local anesthetics delivered epidurally seem safe, and general anesthesia is possible. In their cohort, c-section was a safe option with stimulation switched off during surgery under general anesthesia. They recommend bipolar cautery if needed, not to expose the stimulator and to place the grounding pad distant from DBS hardware to reduce the risk of current spreading through the DBS system and heating the brain tissue surrounding the lead tip [18]. King et al. [19] summarized data on 29 pregnancies and 31 infants exposed to DBS, suggesting a reasonable safety profile, with battery site discomfort being the primary concern. In contrast, our article focused specifically on PD patients, detailing disease management during pregnancy and providing clinical recommendations. Publication bias may skew perceptions, leading to overestimation of treatment effects. We urge the medical community to publish all available data on DBS and pregnancy to ensure unbiased decision-making.

A final consideration may be the role of genetic forms of EOPD and their response to DBS. It is notable that all three published patients have *PRKN*-associated PD. In this scenario, genetic determination and counselling may also be critical for understanding the outcomes and can thus influence the management. Indeed, the effectiveness of DBS is influenced by the underlying genetic mutation causing EOPD, with *SNCA* genomic multiplication responding less well than mutations in the *PRKN* or *PINK1* genes [20, 21].

Based on the limited available data, the EOPD working group suggests the following regarding pregnancy in a PD patient treated with DBS: 1) adequate pregnancy planning with collaboration between the neurologist and obstetrician, as well as with the anesthesiologist later in pregnancy; 2) regular IPG checks before pregnancy and every three months during pregnancy to avoid sudden depletion and battery replacement during the pregnancy; 3) programming is safe during pregnancy and can be performed if needed; 4) vaginal delivery as a preferable choice of delivery; 5) in case of c-section, bipolar cautery should be used as it reduces the potential for electromagnetic interference; 6) breastfeeding should not be discouraged by the presence of the IPG in the breast area.

Addressing this substantial evidence gap for decision-making requires establishing international collaboration to create a pregnancy registry, monitoring the safety of pregnant PD patients and informing guidelines for enhanced care, particularly for women with EOPD. Ensuring the safety of dopaminergic treatment and offering proper advice on treatment

options for PD women are imperative. Establishing an international prospective registry for pregnancy in PD is essential to validate the safety of dopaminergic treatment and provide comprehensive guidance. Local initiatives addressing these needs are ongoing, such as at the School of Medicine at Cardiff and at Radboud University in Nijmegen, The Netherlands. The effort should be made to create international registries.

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DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

REFERENCES

[1] Mocking RJT, Graat I, Denys D (2021) Why has deep brain stimulation had so little impact in psychiatry? *Front Neurol* **12**, 757142.

[2] Deuschl G, Antonini A, Costa J, Śmiłowska K, Berg D, Corvol JC, Fabbrini G, Ferreira J, Foltynie T, Mir P, Schrag A, Seppi K, Taba P, Ruzicka E, Selikhova M, Henschke N, Villanueva G, Moro E (2022) European Academy of Neurology/Movement Disorder Society-European Section Guideline on the Treatment of Parkinson's Disease: I. Invasive Therapies. *Mov Disord* **37**, 1360-1374.

[3] Deuschl G, Antonini A, Costa J, Śmiłowska K, Berg D, Corvol JC, Fabbrini G, Ferreira J, Foltynie T, Mir P, Schrag A, Seppi K, Taba P, Ruzicka E, Selikhova M, Henschke N, Villanueva G, Moro E (2022) European Academy of Neurology/Movement Disorder Society – European Section guideline on the treatment of Parkinson's disease: I. Invasive therapies. *Eur J Neurol* **29**, 2580-2595.

[4] Mehanna R, Smilowska K, Fleisher J, Post B, Hatano T, Pimentel Piemonte ME, Kumar KR, McConvey V, Zhang B, Tan EK, Savica R (2022) Age cutoff for early-onset Parkinson's disease: Recommendations from the International Parkinson and Movement Disorder Society Task Force on Early Onset Parkinson's Disease. *Mov Disord Clin Pract* **9**, 869-878.

[5] Camerucci E, Stang CD, Hajeb M, Turcano P, Mullan AF, Martin P, Ross OA, Bower JH, Mielke MM, Savica R (2021) Early-onset parkinsonism and early-onset Parkinson's dis-

ease: A population-based study (2010–2015). *J Parkinsons Dis* **11**, 1197-1207.

[6] Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP (2005) Progression of motor impairment and disability in Parkinson disease: A population-based study. *Neurology* **65**, 1436-1441.

[7] Ylikotila P, Tiirikka T, Moilanen JS, Kääriäinen H, Marttila R, Majamaa K (2015) Epidemiology of early-onset Parkinson's disease in Finland. *Parkinsonism Relat Disord* **21**, 938-942.

[8] Riboldi GM, Frattini E, Monfrini E, Frucht SJ, Di Fonzo A (2022) A practical approach to early-onset parkinsonism. *J Parkinsons Dis* **12**, 1-26.

[9] Golbe LI (1994) Pregnancy and movement disorders. *Neurol Clin* **12**, 497-508.

[10] Laopaiboon M, Lumbiganon P, Intarut N, Mori R, Ganchimeg T, Vogel JP, Souza JP, Gülmezoglu AM (2014) Advanced maternal age and pregnancy outcomes: A multicountry assessment. *Bjog* **121 Suppl 1**, 49-56.

[11] Young C, Phillips R, Ebenezer L, Zutt R, Peall KJ (2020) Management of Parkinson's disease during pregnancy: Literature review and multidisciplinary input. *Mov Disord Clin Pract* **7**, 419-430.

[12] Vinke RS, Georgiev D, Selvaraj AK, Rahimi T, Bloem BR, Bartels R, Esselink RAJ (2022) Gender distribution in deep brain stimulation for Parkinson's disease: The effect of awake versus asleep surgery. *J Parkinsons Dis* **12**, 1965-1968.

[13] Scelzo E, Mehrkens JH, Bötzel K, Krack P, Mendes A, Chabardès S, Polosan M, Seigneuret E, Moro E, Fraix V (2015) Deep brain stimulation during pregnancy and delivery: Experience from a series of "DBS babies". *Front Neurol* **6**, 191.

[14] Menon PJ, Sambin S, Criniere-Boizet B, Courtin T, Tesson C, Casse F, Ferrien M, Mariani L-L, Carvalho S, Lejeune F-X, Rebbah S, Martet G, Houot M, Lanore A, Mangone G, Roze E, Vidailhet M, Aasly J, Gan Or Z, Yu E, Dauvilliers Y, Zimprich A, Tomantschger V, Pirker W, Álvarez I, Pastor P, Di Fonzo A, Bhatia KP, Magrinelli F, Houlden H, Real R, Quattrone A, Limousin P, Korlipara P, Foltynie T, Grosset D, Williams N, Narendra D, Lin H-P, Jovanovic C, Svetel M, Lynch T, Gallagher A, Vandenberghe W, Gasser T, Brockmann K, Morris HR, Borsche M, Klein C, Corti O, Brice A, Lesage S, Corvol JC, French Parkinson disease Genetics Study Group (PDG) (2024) Genotype–phenotype correlation in PRKN-associated Parkinson's disease. *NPJ Parkinsons Dis* **10**, 72.

[15] Weiss D, Volkmann J, Fasano A, Kühn A, Krack P, Deuschl G (2021) Changing gears – DBS for dopaminergic desensitization in Parkinson's disease? *Ann Neurol* **90**, 699-710.

[16] Dostal M, Weber-Schoendorfer C, Sobesky J, Schaefer C (2013) Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for restless legs syndrome during pregnancy: A case series. *Eur J Neurol* **20**, 1241-1246.

[17] World Health Organization (2017) *Robson classification: Implementation manual*, World Health Organization, Geneva.

[18] Ziman N, Coleman RR, Starr PA, Volz M, Marks WJ, Jr., Walker HC, Guthrie SL, Ostrem JL (2016) Pregnancy in a series of dystonia patients treated with deep brain stimulation: Outcomes and management recommendations. *Stereotact Funct Neurosurg* **94**, 60-65.

[19] King C, Parker TM, Roussos-Ross K, Ramirez-Zamora A, Smulian JC, Okun MS, Wong JK (2022) Safety of deep brain stimulation in pregnancy: A comprehensive review. *Front Hum Neurosci* **16**, 997552.

[20] Pal GD, Hall D, Ouyang B, Phelps J, Alcalay R, Pauciulo MW, Nichols WC, Clark L, Mejia-Santana H, Blasucci L, Goetz CG, Comella C, Colcher A, Gan-Or Z, Rouleau GA, Marder K (2016) Genetic and clinical predictors of deep brain stimulation in young-onset Parkinson's disease. *Mov Disord Clin Pract* **3**, 465-471.

[21] Lohmann E, Welter ML, Fraix V, Krack P, Lesage S, Laine S, Tanguy ML, Houeto JL, Mesnage V, Pollak P, Durr A, Agid Y, Brice A (2008) Are parkin patients particularly suited for deep-brain stimulation? *Mov Disord* **23**, 740-743.