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Intérêt de la neuromodulation sacrée dans les troubles du bas appareil urinaire après chirurgie d'endométriose

Annabelle Aublé

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FACULTE DE MEDECINE ET DE PHARMACIE DE ROUEN

ANNEE 2020

N°

**THESE POUR LE
DOCTORAT EN MEDECINE**

(Diplôme d'Etat)

PAR

Annabelle Aublé

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**Intérêt de la neuromodulation sacrée dans les troubles du
bas appareil urinaire après chirurgie d'endométriose**

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Table of contents

| | |
|---|-----------|
| Remerciements | 14 |
| Préambule | 25 |
| Bibliographie | 33 |
| <i>Evaluation of Sacral Neuromodulation in the Treatment of Low Urinary Tract Dysfunction after Endometriosis Surgery.</i> | 36 |
| Abstract | 37 |
| Introduction | 38 |
| Methods | 39 |
| Results | 41 |
| Discussion | 43 |
| Conclusion | 46 |
| References | 47 |
| Legends | 50 |
| Tables & Figures | 51 |
| <i>Table 1 - Patient characteristics (n=16)</i> | 51 |
| <i>Table 2 – Urodynamics</i> | 52 |
| <i>Table 3 – Univariate analysis of predictive factors of SNM success (n=16)</i> | 53 |
| <i>Figure 1. Flow chart of population (n=16)</i> | 54 |

Préambule

**Intérêt de la neuromodulation sacrée dans les troubles du bas
appareil urinaire après chirurgie d'endométriose**

L'endométriose est une maladie gynécologique fréquente qui concerne une femme sur dix. Elle est liée à la présence de tissu semblable à la muqueuse utérine en dehors de l'utérus (1). Sa définition est histologique. Elle est donc définie comme la présence de tissu endométrial fonctionnel à l'extérieur de l'utérus. Différents organes peuvent être touchés. La maladie peut être asymptomatique. Mais dans d'autres cas, elle peut provoquer des douleurs pelviennes notamment per menstruelles et/ou une infertilité. Bien que décrite pour la première fois en 1927 par Sampson (2), l'endométriose a longtemps été une pathologie mal connue. Les patientes devaient faire face à plusieurs années d'errance diagnostique avant de bénéficier d'une prise en charge adaptée. Depuis une dizaine d'années, du fait de sa médiatisation et de l'implication d'associations de patientes comme Endofrance ou Endomind, elle est rapidement évoquée.

La présentation anatomique de l'endométriose est complexe et hétérogène. Trois types principaux sont identifiés : l'endométriose superficielle, les kystes ovariens revêtus d'endomètre (c'est-à-dire les endométriomes) et les nodules d'endométriose profonde (associés à une pénétration en profondeur de plus de 5 mm de tissu).

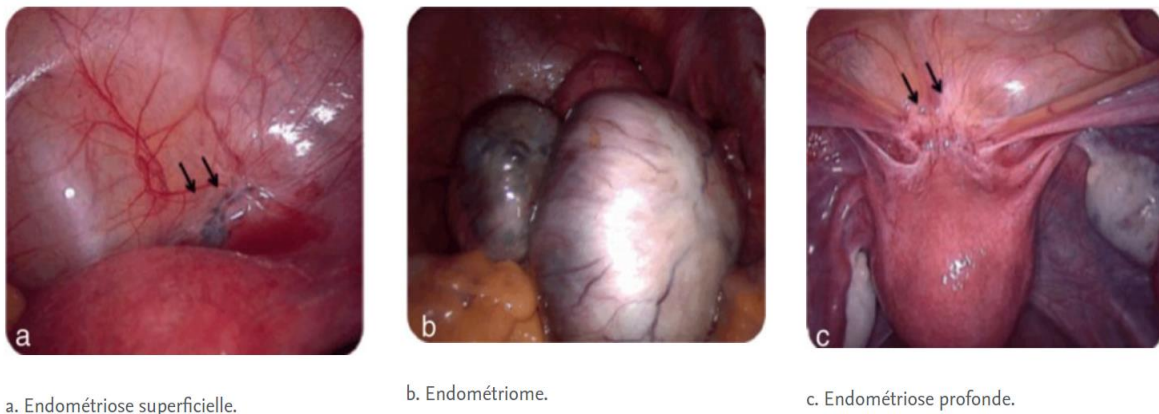


Figure 1 : les différentes formes d'endométriose (Elsevier)

L'endométriose peut toucher tous les organes pelviens mais aussi être localisée en dehors du bassin et atteindre les coupes diaphragmatiques ou le péricarde. En 2016, la World Endometriosis Society a proposé une classification qui comprend la version révisée de l'American Society for Reproductive Medicine (rASRM) (3).



**THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS**

Patient's Name _____ Date _____
 Stage I (Minimal) - 1-5 Laparoscopy _____ Laparotomy _____ Photography _____
 Stage II (Mild) - 6-15 Recommended Treatment _____
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40
 Total _____ Prognosis _____

| PERITONEUM | ENDOMETRIOSIS | < 1cm | 1-5cm | > 5cm |
|---------------------------------|-----------------|-------|-------------------|-----------------|
| | Superficial | 1 | 2 | 4 |
| Deep | 2 | 4 | 6 | |
| R. OVARY | Superficial | 1 | 2 | 4 |
| | Deep | 4 | 16 | 20 |
| L. OVARY | Superficial | 1 | 2 | 4 |
| | Deep | 4 | 16 | 20 |
| POSTERIOR CULDESAC OBLITERATION | Partial | 4 | | 40 |
| | Complete | | | |
| ADHESIONS | < 1/3 Enclosure | | 1/3 2/3 Enclosure | > 2/3 Enclosure |
| | R. Filmy | 1 | 2 | 4 |
| Dense | 4 | 8 | 16 | |
| | L. Filmy | 1 | 2 | 4 |
| Dense | 4 | 8 | 16 | |
| | R. Filmy | 1 | 2 | 4 |
| Dense | 4* | 8* | 16 | |
| | L. Filmy | 1 | 2 | 4 |
| Dense | 4* | 8* | 16 | |

*If the imbedded end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____ Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

EXAMPLES & GUIDELINES

STAGE I (MINIMAL)

PERITONEUM
Superficial Endo - 1-5cm -2

R. OVARY
Superficial Endo - < 1cm -1
Filmy Adhesions - 1/3 -1
TOTAL POINTS -4

STAGE II (MILD)

PERITONEUM
Deep Endo - > 3cm -6

R. OVARY
Superficial Endo - < 1cm -1
Filmy Adhesions - 1/3 -1
L. OVARY
Superficial Endo - < 1cm -1
TOTAL POINTS -9

STAGE III (MODERATE)

PERITONEUM
Deep Endo - > 5cm -6

R. OVARY
CULDESAC -4
L. OVARY
Deep Endo - 1-5cm -16
TOTAL POINTS -26

STAGE III (MODERATE)

PERITONEUM
Superficial Endo - > 5cm -5

R. TUBE
Filmy Adhesions - < 1/3 -1

R. OVARY
Filmy Adhesions - < 1/3 -1

L. TUBE
Dense Adhesions - < 1/3 -16*

L. OVARY
Deep Endo - < 1cm -4
Dense Adhesions - < 1/3 -4
TOTAL POINTS -29

STAGE IV (SEVERE)

PERITONEUM
Superficial Endo - > 5cm -5

L. OVARY
Deep Endo - 1-5cm -32**
Dense Adhesions - < 1/3 -8**

L. TUBE
Dense Adhesions - < 1/3 -8**
TOTAL POINTS -51

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)

PERITONEUM
Deep Endo - > 5cm -6

CULDESAC
Complete Obliteration -40

R. OVARY
Deep Endo - 1-5cm -16
Dense Adhesions - < 1/3 -4

L. TUBE
Dense Adhesions - > 2/3 -16

L. OVARY
Deep Endo - 1-5cm -16
Dense Adhesions - > 2/3 -16
TOTAL POINTS -114

Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 7). A 4cm deep endometrioma of the ovary associated with more than 3cm of superficial disease should be scored 20 (not 24).

In those patients with only one adnexa, points applied to disease of the remaining tube and ovary should be multiplied by two. *Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe).

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, leiomyomata, uterine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and means of observation (laparoscopy or laparotomy) should be noted.

Figure 2. American Society for Reproductive Medicine revised classification. (3)

Les lésions endométriosiques peuvent être identifiées de manière fiable par échographie transvaginale ou par imagerie par résonance magnétique (IRM), avec une sensibilité et une spécificité de plus de 90 % (4).

| Table 1 Ultrasound features of endometriosis | |
|---|--|
| Pathology | Ultrasonographic Characteristics |
| Adenomyosis | <ul style="list-style-type: none"> • Globular shape • Enlarged dimensions of the uterus • Uterine wall asymmetry unrelated to leiomyoma • Presence of an indistinctly defined area with either decreased or increased echogenicity • Hypoechoic linear striations • Round anechoic areas of 1–7 mm diameter (myometrial cysts) • Adenomyotic lesion • Irregularities of the endometrial-myometrial junctional zone |
| Endometrioma | <ul style="list-style-type: none"> • Unilocular cyst (most commonly), multilocular, unilocular-solid, multilocular-solid (less commonly) • Ground-glass content • No vascularization on color Doppler |
| Deep infiltrating endometriosis | <ul style="list-style-type: none"> • Hypoechoic lesion with or without regular contours • Hourglass-shaped or diabolo-like nodule appearance • Comet nodule appearance • Indian headdress sign • Thickened and hyperechoic uterosacral ligaments |
| Decidualized endometrioma | <ul style="list-style-type: none"> • Unilocular-solid or multilocular-solid • Ground-glass or low-level cyst content • Rounded papillary projections with smooth surface • Well vascularized |

Tableau 1 : Caractéristiques échographiques de l'endométriose (5)

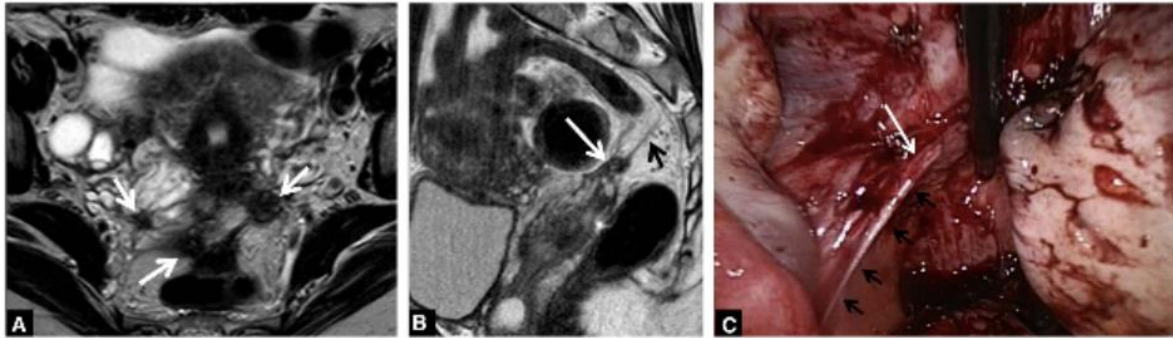


Figure 4. Aspects d'endométriose profonde en IRM (6)

Femme de 43 ans atteinte d'endométriose infiltrante profonde. A. image IRM pondérée en T2 dans le plan axial montrant un nodule d'endométriose typique avec une atteinte du ligament utérosacré dans sa portion distale (flèche blanche). B. image IRM pondérée T2 correspondante au plan axial du ligament utérosacré (la flèche blanche pointe la lésion, la flèche noire la proportion normale du ligament). C. Confirmation en laparoscopie de la présence de lésions d'endométriose sur le ligament utérosacré (flèche blanche) et ligament utérosacré droit non atteint (flèche noire).

Toutefois, selon le groupe de spécialistes sur l'endométriose de la Société Européenne de Reproduction Humaine et d'Embryologie (ESHRE), le diagnostic de l'endométriose profonde nécessite une exploration chirurgicale, qui constitue l'investigation de référence, pour évaluer l'extension de la maladie, visualiser et localiser les lésions et évaluer la profondeur d'infiltration en effectuant des biopsies (7).

La prévalence de l'endométriose est difficile à déterminer avec précision, du fait de la nécessité d'une exploration chirurgicale pour en faire le diagnostic définitif. On estime que l'endométriose touche 10 % des femmes en âge de procréer (8). La présentation clinique est très hétérogène et n'est pas toujours corrélée à la classification ASRM (9). L'endométriose peut être asymptomatique ou associée à une dysménorrhée, des douleurs pelviennes chroniques, une dyspareunie, une infertilité (10), de la fatigue (11), une dyschésie ou une dysurie. L'endométriose est présente chez 21 à 47 % des femmes présentant une infertilité et chez 71 à 87 % de celles qui souffrent de douleurs pelviennes chroniques (12). L'endométriose infiltrante profonde peut représenter 2 % de tous les cas (13) et entraîner des symptômes plus graves que l'endométriose superficielle, notamment une dysménorrhée importante et une infertilité plus fréquente (14).

Les mécanismes qui conduisent à l'endométriose restent mal connus. Toutefois, l'hypothèse principale est celle de l'implantation de matériel utérin provenant de menstruations rétrogrades (2). Au cours des règles, du sang provenant des trompes parvient à la cavité

abdominale en transportant avec lui des fragments d'endomètre, voire des cellules pluripotentes capables de générer de nouveaux foyers d'endométriose (12).

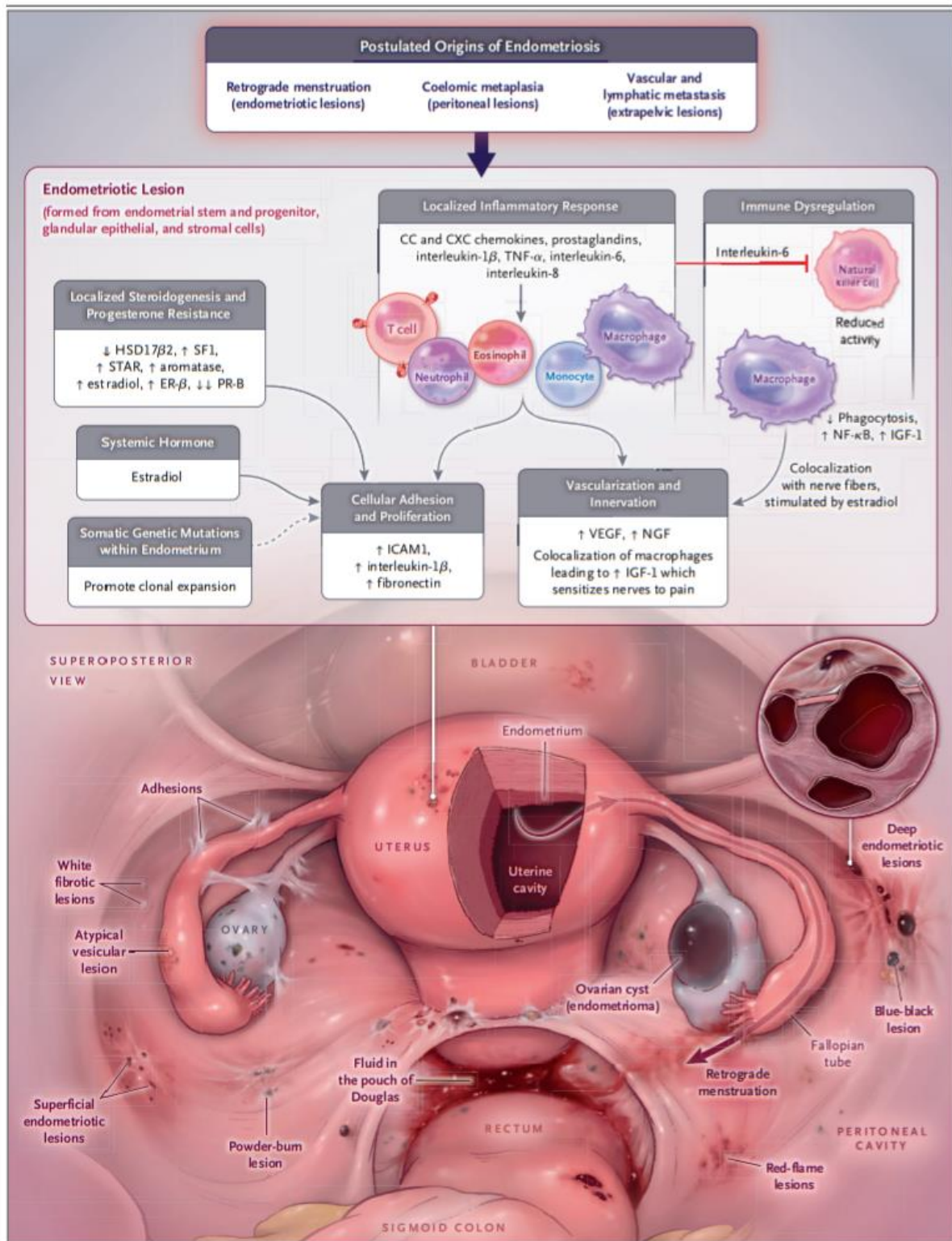


Figure 5 : Pistes potentielles pour la pathogénie et la physiopathologie de l'endométriose pelvienne (12)

Néanmoins, alors que les cliniciens estiment que 90% des femmes présentent des saignements rétrogrades, seules 10% d'entre elles développent des lésions d'endométriose. Des facteurs de susceptibilité individuelle interviennent dans le développement de cette maladie. L'exposition aux menstruations (premières règles précoces, volume menstruel important, cycles courts) est associée à la présence d'endométriose. Le risque de développer une endométriose pour les apparentées au premier degré est cinq fois plus élevé que dans la population générale. Des facteurs génétiques pourraient être impliqués (15). Une revue d'études épigénétiques a montré des différences de méthylation de l'ADN (modifications chimiques qui entraînent des différences dans l'expression des gènes) entre les cellules qui composent les lésions et celles de l'endomètre des patientes, en particulier aux extrémités des chromosomes (16). Ce phénomène est associé à des formes particulières de l'enzyme DNMT3L (de la famille des méthyl-transférases de l'ADN) (17). Une de ces formes multiplie par sept le risque de développer la maladie. Elle pourrait donc servir d'outil pour le diagnostic de la maladie et son pronostic. Des facteurs environnementaux, comme les perturbateurs endocriniens, seraient également mis en jeu via les modulations épigénétiques qu'ils pourraient provoquer.

L'appareil urinaire peut également être le siège de lésions endométriosiques. L'endométriose de la vessie est rare (18). La localisation urétérale est la plus fréquente. Sa prévalence est d'environ 1 %, mais elle passe à plus de 50 % chez les patientes atteintes d'endométriose profonde (19). Le traitement de l'endométriose vésicale nécessite généralement une approche cystoscopique et laparoscopique combinée pour effectuer une excision complète (20). Cette stratégie permet d'épargner le tissu vésical sain et d'éviter une réduction iatrogène de la capacité vésicale. L'endométriose urétérale est associée à d'autres localisations dans presque 90 % des cas, mais elle est également asymptomatique chez 30 % des patientes. L'endométriose peut alors entraîner une obstruction urétérale. Elle nécessite alors une approche chirurgicale, l'urétérolyse avec ou sans urétérectomie segmentaire, pour protéger les voies urinaires supérieures et préserver la fonction rénale (21).

Cependant, des troubles du bas appareil urinaire (TUBA) sont fréquemment rapportés par les patientes après une intervention pour endométriose alors qu'aucune exérèse n'a concerné l'appareil urinaire. En effet, l'incidence des TUBA varie de 3,4 % à 15,4 % chez les femmes ayant subi une chirurgie d'endométriose profonde (19). Les TUBA font partie des complications les plus fréquentes après chirurgie d'endométriose profonde. L'incidence des

symptômes urinaires postopératoires varie selon les études. Bonneau et al. ont rapporté des troubles de la miction de novo allant jusqu'à 30 % (22). Ballester et al ont constaté que 29 % des patientes qui présentaient une dysurie post-opératoire avaient recours aux autosondages intermittents propres à 3 mois de la chirurgie (19). La nécessité d'une colpectomie partielle, d'une paramérectomie et/ou d'une résection digestive avec anastomose colo-anales était associée à un plus grand risque de troubles mictionnels postopératoires (22).

La physiopathologie des troubles mictionnels dans l'endométriose implique plusieurs mécanismes : infiltration du plexus hypogastrique par des lésions d'endométriose, en combinaison avec des phénomènes inflammatoires ou des atteintes du plexus hypogastrique inférieur par la chirurgie de l'endométriose elle-même (21). Un mécanisme de viscérosensibilisation croisée a également été évoqué. Chez les femmes atteintes d'endométriose, un taux plus élevé de contraction paradoxale du levator ani a été constaté lors de l'échographie pelvienne (23), ce qui suggère le rôle des voies nerveuses croisées dans le bassin endométriosique.

Les chirurgiens spécialistes de l'endométriose ont mis au point des techniques spécifiques pour réduire les complications postopératoires. Après une chirurgie d'endométriose profonde, le taux de complications urinaires est plus fréquent en laparotomie qu'en approche laparoscopique, par voie robot assistée ou non (24). Ce sont surtout les techniques de préservation des nerfs pelviens qui préviennent les complications urinaires et le recours aux autosondages (25). Malgré tout, le trouble de vidange reste une complication significative qui peut aller jusqu'à près de 15% des cas, avec une dégradation certaine de la qualité de vie (22).

La seule alternative aux autosondages intermittents en cas de trouble de la vidange vésicale est la neuromodulation des racines sacrées. Ainsi, nous nous sommes intéressés à l'efficacité de la neuromodulation sacrée dans les troubles de vidange post-opératoires d'une chirurgie d'endométriose.

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**Evaluation of Sacral Neuromodulation in the Treatment of Low
Urinary Tract Dysfunction after Endometriosis Surgery.**

Abstract

Title: Evaluation of Sacral Neuromodulation in the Treatment of Low Urinary Tract Dysfunction after Endometriosis Surgery.

Introduction: The most frequent complication of pelvic surgery of endometriosis is voiding dysfunction (VD). Sacral neuromodulation (SNM) had shown its effectiveness in the treatment of overactive bladder (OAB) and non-obstructive retention (NOR).

The objective of this study was to evaluate the effectiveness of SNM in patients who suffered of LUTD after endometriosis surgery.

Methods: A monocentric retrospective study was conducted from January 2011 to October 2019. All patients in whom a SNM testing was performed after one or more endometriosis surgeries, were included. Clinical data were collected from medical records. All SNM tests were performed according to International Continence Society best practice statement. An improvement of more than 50% of the symptoms allowed the implantation of the pulse generator (Interstim 2™, Medtronic, USA).

Results: During the period, 16 patients were enrolled. Eleven patients had undergone deep infiltrating endometriosis (DIE) surgery. The median interval time between last endometriosis surgery and SNM test was 21.5 months [15.8 – 45.8]. Eight patients performed clean intermittent self-catheterization (CISC). Ten patients had a significant post-void residual (PVR), with a mean PVR volume at 218.6 (\pm 123.3) ml. Fourteen patients were implanted. After a median follow-up of 23 (1 – 43) months, 10 patients were always treated by SNM. Moreover, 3 patients were weaned from CISC. DIE surgery was not a predictive factor of failure of SNM, either than perform CISC.

Conclusion: To our knowledge, our study reports the results of the largest series of patients treated with SNM after endometriosis surgery. SNM is an effective treatment of LUTD and allows weaning of CISC in some cases. The success rate of this study offers an interesting perspective to these young patients with limited therapeutic options.

Key words: Sacral Neuromodulation – Endometriosis – Low Urinary Tract Dysfunction – Low Urinary Tract Symptoms – Voiding Dysfunction

Introduction

Endometriosis is defined as the presence of endometrium-like tissue outside the uterus (1). Anatomical presentation of endometriosis is complex and heterogeneous. Three main types are identified: superficial implantation on the peritoneum, endometrial lined ovarian cysts (i.e. endometriomas), and endometriotic nodules (usually associated with in-depth penetration of more than 5mm of tissue) (2). Endometriosis can be located outside the pelvis. In 2016, World Endometriosis Society has proposed a classification toolbox that includes the revised American Society for Reproductive Medicine (rASRM) (3).

According to the European Society for Human Reproduction and Embryology (ESHRE) Special Interest Group for Endometriosis surgical exploration is required for the definitive diagnosis (4). Endometriosis is estimated to affect 10% of reproductive-age women (5). Clinical presentation is very heterogeneous and not always correlated to rASRM staging classification (6). Endometriosis can be asymptomatic (7) or associated to dysmenorrhea, chronic pelvic pain, dyspareunia, infertility (8), fatigue (9), dyschesia or dysuria. Deep infiltrating endometriosis (DIE) may represent 2% of all cases (10) and is related to more severe symptoms compared to superficial endometriosis (11), including severe dysmenorrhea and infertility.

The treatment of DIE is a complex surgery with extensive and complete resection of all endometriosis, with a risk of injury of adjacent organs. Despite nerve technique preservation, one of the most important urological complications of major gynecologic surgeries for DIE management is urinary retention sometimes requiring short term catheterization with spontaneous recovery (transient retention), sometimes requiring prolonged bladder catheterization or clean intermittent self-catheterization (CISC) (12).

For persistent long-term voiding dysfunction, CISC is the gold standard. However, sacral neuromodulation (SNM) has proven its efficacy in lower urinary tract dysfunctions (LUTD), including voiding dysfunction. SNM is indeed validated in overactive bladder (pollakiuria with or without urinary incontinence with urgency) refractory to conservative treatment and in chronic urinary retention with functional bladder outlet obstruction due to sphincter dyssynergia without urological obstruction refractory to conservative treatment. Thus, SNM is a possible treatment option for chronic voiding dysfunction after endometriosis surgery. A first study of 5 case series was published in literature about the interest of SNM in management of VD after DIE surgery (14).

The aim of our study was to assess the effectiveness of SNM in VD women after endometriosis surgery in larger cohort in expert centre.

Methods

Study design

A monocentric retrospective study was conducted from January 2011 to October 2019. All patients referred for chronic bladder dysfunction after surgical endometriosis management who undergone a SNM test were included. Patients were identified through a database using PMSI (Programme de Médicalisation - Système d'information) coding system (AHLA003 and AHLB018). Clinical data were collected by review of medical records. The study was performed in accordance with the Declaration of Helsinki.

SNM procedure

SNM procedures were performed according to International Continence Society best practice statement (15). SNM procedure was conducted as recommended as a two steps procedure, including a test phase, (lead implantation with clinical evaluation of efficacy) and a subsequent implantation of the device or explantation of the lead. The first procedure (lead placement) was conducted under general anaesthesia in all cases. All patients were in prone position with exposition of the anus in the operating field. Tine lead (Interstim™, MedTronic, Minneapolis, USA) was positioned in sacral foramen S3 or S4 under fluoroscopic control. The correct position of the lead was checked by X-ray and evaluation of motor response. A plantar flexion of hallux and/or an anal sphincter contraction were considered as a positive motor response. The lead was connected to a temporary external generator for the test phase. Patients attended office visits after surgery after a 2-week period, with evaluation of bladder diary. During the test phase, an improvement of more than 50% of the criteria allowed the implantation of definitive generator. For each patient, the definitive implantation criteria were defined before the lead implantation. Implantation criteria were as follows: improvement of dysuria, micturition without straining to void, decrease of post-voiding residual volume, recovery of spontaneous micturition, weaning of ISC. It could be single or composite criteria according to the patient's complaint and purpose. Implantations of definitive generator were performed under local or general anaesthesia. Patients were followed according to routine practice.

Data collection

Patient characteristics were collected: age, body mass index, superficial or deep endometriosis, localization of lesions, type of endometriosis surgery, diabetes, anorectal disorders, previous urological surgery, low urinary tract symptoms, urodynamics studies (UDS), perioperative data of SNM procedures and follow-up data. The follow-up was continued until August 2020.

The primary outcome was the percentage of patients successfully treated by SNM at the end of follow-up. Success was defined by an improvement of 50% or more of preoperative criteria of the implantation criteria. After implantation, SNM failure occurred when patients reported less than 50% improvement of baseline voiding function, or worsening of the symptoms, or if they needed to redo CISC despite neurostimulator reprogramming. In case of SNM failure, we noticed clinical evolution of patients and treatment at the final visit of the follow-up. Complications were reported such as device infections or dysfunctions which required surgical revisions, and implant site pain or paresthesias.

Statistical analysis

Data are expressed in mean \pm standard deviation (SD) or median [first interquartile – third interquartile]. A Fisher's exact test was performed to analyse contingency tables. Data were analysed using Prism 8.0 from Graph Pad Software. A p value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

From January 2011 to October 2019, 16 women were included. Patient characteristics are shown in Table 1. The mean age at the time of SNM test was 34.1 (\pm 7.3) years. There were no diabetic women. Patients reported anorectal disorders in 9 cases. Four patients had undergone previous urological surgery: bladder biopsies (n=2), bladder hydrodistension (n=2) for bladder pain syndrome, meatotomy (n=1). Eleven patients had undergone DIE surgery. Hysterectomy was performed in 5 patients. Seven patients underwent multiple surgical procedures. The median interval time between last endometriosis surgery and SNM test was 21.5 months [15.8 – 45.8].

All patients reported dysuria. Fourteen patients were able to have spontaneous micturition but most of the time with straining to void. Ten patients had a significant post-void residual (PVR). Eight patients performed CISC. Some patients had others LUTS, such as urgency or stress urinary incontinence.

Urodynamic studies

Data of UDS were not available for all patients (Table 2). For 4 patients who performed CISC, uroflowmetry was preoperatively not assessed. Among 12 available uroflowmetry studies, 2 were not usable because of total urine volume was less than 150ml. For a mean voiding volume of 285.5 (\pm 181.1) ml, the mean PVR volume was 218.6 (\pm 123.3) ml. The mean maximum flow rate was 16.7 (\pm 8.6) ml/s.

Two patients were not assessed by urodynamic study. One cystomanometry had to be stopped because the patient did not support bladder filling. All parameters were not available for the 13 remaining UDS. None of the patients had bladder compliance disorder. One patient had terminal detrusor overactivity. Only 5 patients had a pressure flow study. The mean maximum flow rate was 12.7 ml/s with a mean detrusor pressure at maximal flow at 28.25 cm H₂O. Six patients failed to perform micturition on urodynamic table. In profilometry, pressure values were normal for age with a mean maximum urethral closure pressure (MUCP) at 99.8 (\pm 27.1) cm H₂O. No patient had a MUCP more than 130 cm H₂O.

Success of SNM

After a median follow-up of 23 (1 – 43) months, 10 patients were always treated by SNM at the end of follow-up (Figure 1). Among 8 patients who performed ISC before SNM

test, 3 women were weaned off ISC. The mean stimulation intensity of definitive generator was 2 (\pm 1.4) mA at the end of follow-up.

One patient had to always perform CISC but decreased the number of CISC and SNM improved her quality of life. A secondary loss of effectiveness had appeared in 1 patient associated with site implant pain which required explantation. One patient whom intraoperative stimulation was a failure, always performed CISC. One patient turned off her stimulator for pregnancy and has been lost of follow-up since. One patient had to undergo surgical revision for device infection.

Predictive factors of success or failure

The only identified predictive factor of SNM success was deep infiltrating endometriosis surgery with OR = 0.06 (0.0042 – 0.8784; p=0.04). Other factors are described in Table 3. Perform CISC was not a predictive factor of SNM failure. The mean intensity of stimulation during the testing phase was not associated with success or failure of definitive SNM.

Complications and surgical revisions

Two first electrode placements were complicated by infection of the device requiring explantation. One of them reoffended after definitive implantation whereas an interval of almost 5 months had been respected and under the guise of an appropriate antibiotic prophylaxis. One other infection occurred after first generator implantation.

Implant site pain have appeared in 5 patients requiring 2 surgical revisions and one explantation. One system failure required a surgical revision and generator change. Lower limb paresthesias were reported by 2 patients.

Discussion

The long-term success rate of SNM, at 5 years, is over 70% in overactive bladder or urinary chronic retention (16). Moreover, the best long-term cure rate (54%) is observed in retention patients (17). SNM is currently the only alternative therapeutic for women with severe voiding dysfunction which required CISC.

In our study, SNM was a good therapeutic option for low urinary tract dysfunction after endometriosis surgery. After a median follow-up of 23 months, more than 50% of patients were always treated by SNM with a subjective good reported satisfaction of quality of life. Furthermore, 3 patients were weaned off CISC among 8 patients who previously performed CISC.

Our study is the largest cohort in literature. Two previous studies had described the interest of SNM in LUTS after endometriosis surgery. In 2015, Nyangoh Timoh et al. reported 5 case series (14). Two patients were improved by SNM with a median follow-up of 40 months. One patient was weaned off CISC and one decreased CISC at twice a day. A larger retrospective study was recently published by Agnello et al. in August 2020 in women suffering voiding dysfunction after DIE surgery (18). After the testing period, 9 of 13 patients (69%) reported a significant improvement of their symptoms and were definitively implanted.

These two previous studies suggested to wait more than one year to treat voiding dysfunction after endometriosis surgery (14,18). We also proposed SNM for persistent LUTS. In our study, the median time between endometriosis surgery and SNM test was 21 months. No patient in our cohort had spontaneous improvement of LUTS one year after endometriosis surgery. We consider patients improvement observed at the end of follow-up is due to SNM effectiveness and not due to spontaneous improvement. Moreover, SNM success at the end of follow-up was not different according to the interval between endometriosis surgery and SNM testing.

We observed 6 failures. One patient was lost of follow-up after pregnancy. Among 2 patients reported a secondary loss of effectiveness of SNM, one chose to be explanted because of implant site pain and another had to reperform CISC for significant PVR whereas she was weaned off during testing phase. This patient could not increase the intensity of stimulation because of paresthesia in lower limbs. One patient had recurrent device infection and, in accordance with her, was not implanted whereas SNM improved significant PVR, and finally prefers to continue CISC. No per-operative response occurred in one patient. This patient presented a severe voiding dysfunction with no spontaneous micturition and performed CISC. She had 4 previous surgeries for extended DIE with damage of sacral roots. One another patient

had a negative testing phase with no improvement of significant PVR which required CISC. This patient also presented a severe DIE with hypogastric nerve damage. We observed that no patient with no spontaneous micturition had SNM success.

Physiopathology of urinary dysfunctions in endometriosis involves several mechanisms: infiltration of the hypogastric plexus by endometriosis lesions, in combination with inflammatory phenomena or damages caused to the inferior hypogastric plexus by pelvic endometriosis surgery (19). LUTS belong to the more frequent complications after DIE surgeries. The incidence of LUTS varies from 3.4% up to 15.4% in women with posterior DIE without urinary tract endometriosis (20). Bonneau et al. reported de novo voiding dysfunction up to 30% (21). Ballester et al. found 29% of dysuria with need to perform CISC with a mean duration of 3 months (20). Risk factors of postoperative urinary dysfunction are partial colectomy, parametrectomy and patients requiring colo-anal anastomosis (21). Endometriosis expert surgeons developed specific techniques to decrease postoperative complications. After DIE surgery, the rate of urinary complications is more frequent in laparotomy than laparoscopic approach, with no difference between robot-assisted laparoscopic approach and laparoscopy (22). However, nerve-sparing techniques in surgeries for DIE prevent urinary complications and need of CISC (23). Despite these advances, persistent urinary retention (UR) remains a significant complication which ranges from 0 to 14.7%, with quality of life impairment (21).

Severity of DIE could be expected as a predictive factor of SNM failure. On the contrary, according to our data, it was a significant predictive factor of SNM success. This result could be explained by a centre effect bias. Our patients were treated in a tertiary expert centre of endometriosis management. Surgical procedures were performed by expert surgeons who described conservative and nerve-sparing techniques (24). Moreover, urinary and digestive post-operative complications were both cared by expert teams. Among our 9 patients who reported concomitant anorectal disorders, 3 were spontaneously reported an improvement of digestive disorders after SNM implantation for LUTS, which may have increased their global satisfaction.

Voiding dysfunction can result by detrusor underactivity, bladder outlet obstruction, or both (25). A mechanism of viscerosensitization has also been evocated to explain LUTD observed in endometriosis. In endometriosis women with VD, a higher rate of levator ani paradoxal contraction was found in pelvic ultrasound (26), suggesting the role of cross talk nerve pathways in endometriotic pelvis. Although the mechanism of SNM is not totally elucidated, it seems to involve modulation of spinal cord reflexes and brain networks by peripheral sensory and possibly motor neurons (27). Since a long time, SNM improves women

with disorder of urethral sphincter relaxation like in Fowler's syndrome (28). Moreover, in another urodynamic study, SNM seems to increase the bladder contractility rather than increase urethral sphincter relaxation (29).

Due to a retrospective study design, we unfortunately have missing data about preoperative urodynamic assessment. Moreover, EMG is not always performed for LUTD assessment in our centre. Urodynamic study and EMG are invasive explorations. We did not assess patients after implantation of SNM. We could not compare and comment the effects of SNM on these parameters. Agnello et al. reported 4 failures of SNM in their study. Patients were heterogeneous: 3 patients had functional bladder outlet obstruction and one had bladder acontractility. Half patients had multiple endometriosis surgery whereas half had one surgery. Among two patients who were evaluated by EMG, one had a bilateral pudendal neuropathy whereas one had a normal perineal EMG. Their results did not reveal any factors predictive of success or failure of SNM, and confirm that several physiopathologic mechanisms are involved in voiding dysfunction after DIE surgery.

SNM has proven its effectiveness in several functional pelvic disorders, and also in chronic pelvic pain syndrome (30). Lavonius et al. tested SNM and reported better quality of life for four endometriosis women who suffered of chronic pelvic pain after surgery (31). Their results were confirmed in larger Finnish national cohort, with 75% of success rate (32). The improvement of pelvic pain may also increase global satisfaction of our patients.

SNM appears to be a very promising treatment for endometriosis patients who could suffer of LUTD, anorectal disorders or chronic pelvic pain syndrome. Management of endometriosis disease requires multidisciplinary team. Surgical approach may have to validate in concerted mitting (33). We consider that SNM may be proposed to all patients who present persistent LUTD after endometriosis surgery by multidisciplinary specialist team of pelviperineology.

Conclusion

In this study, we reported the interest of SNM in the largest cohort of women with voiding dysfunction after endometriosis surgery. Our results suggest that SNM is a promising treatment for several functional pelvic disorders in endometriotic women: LUTD, anorectal disorders and chronic pelvic pain syndrome. Moreover, SNM appears like the only alternative treatment to avoid long-term CISC.

We failed to identify clinical or urodynamic predictive factors of success of SNM. Other study with a larger cohort is necessary to understand it. The most important challenge is to shed light on involved mechanisms: improvement of bladder contractility, modulation of peripheral sensitive afferences and their brain control, or action on functional bladder outlet obstruction.

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Legends

Table 1. Patients characteristics (n=16)

BMI: body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology collaboration equation; LUTS: low urinary tract symptoms; CISC: clean intermittent self-catheterization

*number of concerned patients; [n=] number of patients whom data were available

Note: Results are expressed in mean and standard deviation or median and interval range

Table 2. Urodynamics

*number of concerned patients; [n=] number of patients whom data were available

Note: Results are expressed in mean and standard deviation or median and interval range

Table 3. Univariate analysis of predictive factors of SNM success (n=16)

^α: Baptisa-Pike test; ^β: Fisher's exact test

DIE: deep infiltrating endometriosis; SNM: sacral neuromodulation; PVR: post-void residual;

CISC: clean intermittent self-catheterization

Figure 1. Flow chart of population (n=16)

TP: test phase; SNM: sacral neuromodulation; QoL: quality of life; CISC: clean intermittent self-catheterization; PVR: post-void residual

Tables & Figures

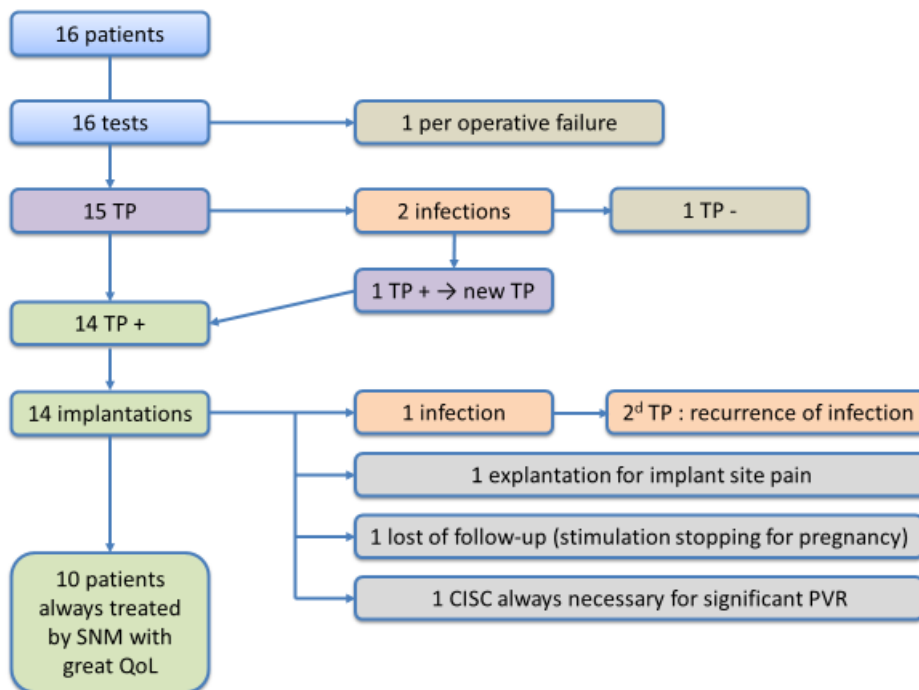
| Table 1 - Patient characteristics (n=16) | |
|---|------------------|
| General characteristics and comorbidities | |
| Age, mean \pm SD (year) | 34.1 \pm 7.3 |
| BMI, mean \pm SD (kg/m ²) | 25.2 \pm 4.8 |
| Diabetes * | 0 |
| Constipation or dyschezia * | 9 |
| Estimated glomerular filtration rate (CKD-EPI), mean \pm SD (ml/min/1.73m ²) [n=11] | 103.9 \pm 14 |
| Previous urologic surgery * | 4 |
| Characteristics of endometriosis disease & surgery | |
| Bilateral localization of endometriosis lesions | 9 |
| Deep infiltrating endometriosis * | 11 |
| Digestive surgery * | 10 |
| Rectal surgery * | 9 |
| Sigmoid surgery * | 5 |
| Digestive stomia * | 3 |
| Hysterectomy * | 4 |
| Ureterolysis * | 5 |
| Ureterovesical reimplantation * | 1 |
| Number of endometriosis surgery | |
| 1 * | 9 |
| 2 * | 4 |
| \geq 3 * | 3 |
| Median interval between endometriosis surgery and SNM test (month) | 21.5 (13 – 45.8) |
| LUTS | |
| Dysuria * | 16 |
| Spontaneous micturition * | 14 |
| Straining to void * | 13 |
| Significant post-void residual * | 10 |
| Need to perform CISC * | 8 |
| Urgency * | 5 |
| Stress urinary incontinence * | 3 |
| Recurrent urinary tract infections * | 7 |

| Table 2 – Urodynamics | |
|---|-------------------|
| Uroflowmetry [n=10] | |
| Voiding volume, mean \pm SD (ml) | 285.5 \pm 181.1 |
| Post-void residual volume, mean \pm SD (ml) [n=8] | 218.6 \pm 123.3 |
| Voiding time, mean \pm SD (s) | 55.5 \pm 36.7 |
| Maximum flow rate, mean \pm SD (ml/s) | 16.7 \pm 8.6 |
| Mean flow rate, mean \pm SD (ml/s) | 7 \pm 5.2 |
| Cystomanometry [n=13] | |
| Basal bladder pressure, mean \pm SD (cm H ₂ O) [n=8] | 14 \pm 6.4 |
| Maximum bladder pressure, mean \pm SD (cm H ₂ O) [n=7] | 32.3 \pm 9.2 |
| Cystometric capacity, mean \pm SD (ml) [n=10] | 448.7 \pm 152.7 |
| First sensation of bladder filling | |
| Bladder pressure, mean \pm SD (cm H ₂ O) [n=7] | 19,1 \pm 6 |
| Bladder volume, mean \pm SD (ml) [n=11] | 230.9 \pm 179.3 |
| First desire to void | |
| Bladder pressure, mean \pm SD (cm H ₂ O) [n=5] | 17.4 \pm 5.6 |
| Bladder volume, mean \pm SD (ml) [n=8] | 240.1 \pm 124.8 |
| Strong desire to void | |
| Bladder pressure, mean \pm SD (cm H ₂ O) [n=4] | 19.3 \pm 5.6 |
| Bladder volume, mean \pm SD (ml) [n=7] | 320.6 \pm 153.1 |
| Bladder pain | |
| Bladder pressure, mean \pm SD (cm H ₂ O) [n=6] | 20.2 \pm 5.6 |
| Bladder volume, mean \pm SD (ml) [n=6] | 356 \pm 179.5 |
| Detrusor overactivity * | |
| | 1 |
| Pressure flow study [n=5] | |
| Maximum flow rate, mean \pm SD (ml/s) [n=5] | 12.7 \pm 11 |
| Detrusor pressure at maximal flow, mean \pm SD (cm H ₂ O) [n=4] | 28.25 \pm 13.5 |
| Urethral pressure measurement [n=10] | |
| Mean maximum urethral pressure, mean \pm SD (cm H ₂ O) [n=10] | 110.5 \pm 18.5 |
| Mean maximum urethral closure pressure, mean \pm SD (cm H ₂ O) [n=9] | 99.8 \pm 27.1 |
| Mean functional profile length, mean \pm SD (mm) [n=9] | 32.7 \pm 3.5 |

Table 3 – Univariate analysis of predictive factors of SNM success (n=16)

| Variables | Odds ratio (95% CI) ^a | P-value ^β |
|--|----------------------------------|----------------------|
| DIE surgery | 0.06 (0.0042 – 0.8784) | 0.0357 |
| Multiple endometriosis surgery | 0.50 (0.0727 – 4.409) | 0.63 |
| Interval > 24 months between last endometriosis surgery and SNM test | 0.50 (0.0727 – 4.409) | 0.63 |
| Pre-operative significant PVR | 2.33 (0.3501 – 14.62) | 0.61 |
| Perform CISC | 0.33 (0.0492 – 2.893) | 0.61 |
| Pre-operative Q max < 15 ml/s | 2.00 (0.2453 – 16.28) | >0.99 |

Figure 1. Flow chart of population (n=16)



Title: Evaluation of Sacral Neuromodulation in the Treatment of Low Urinary Tract Dysfunction after Endometriosis Surgery.

Introduction: The most frequent complication of pelvic surgery of endometriosis is voiding dysfunction (VD). Sacral neuromodulation (SNM) had shown its effectiveness in the treatment of overactive bladder (OAB) and non-obstructive retention (NOR).

The objective of this study was to evaluate the effectiveness of SNM in patients who suffered of LUTD after endometriosis surgery.

Methods: A monocentric retrospective study was conducted from January 2011 to October 2019. All patients in whom a SNM testing was performed after one or more endometriosis surgeries, were included. Clinical data were collected from medical records. All SNM tests were performed according to International Continence Society best practice statement. An improvement of more than 50% of the symptoms allowed the implantation of the pulse generator (Interstim 2™, Medtronic, USA).

Results: During the period, 16 patients were enrolled. Eleven patients had undergone deep infiltrating endometriosis (DIE) surgery. The median interval time between last endometriosis surgery and SNM test was 21.5 months [15.8 – 45.8]. Eight patients performed clean intermittent self-catheterization (CISC). Ten patients had a significant post-void residual (PVR), with a mean PVR volume at 218.6 (\pm 123.3) ml. Fourteen patients were implanted. After a median follow-up of 23 (1 – 43) months, 10 patients were always treated by SNM. Moreover, 3 patients were weaned from CISC. DIE surgery was not a predictive factor of failure of SNM, either than perform CISC.

Conclusion: To our knowledge, our study reports the results of the largest series of patients treated with SNM after endometriosis surgery. SNM is an effective treatment of LUTD and allows weaning of CISC in some cases. The success rate of this study offers an interesting perspective to these young patients with limited therapeutic options.

Key words: Sacral Neuromodulation – Endometriosis – Low Urinary Tract Dysfunction – Low Urinary Tract Symptoms – Voiding Dysfunction