Botulinum toxin A (Botox) injection into muscles of pelvic floor as a treatment for persistent pelvic pain secondary to pelvic floor muscular spasm – A Pilot Study

Short running title:

Botox injection for persistent pelvic pain

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MeSH keywords:

Botulinum Toxins, Type A

Pelvic pain

Pelvic floor

Quality of life

Spasm

Manuscript word count: 2481

Abstract word count: 249

Figure count: 2

Table count: 2

Acknowledgments:
We acknowledge the contributions to recruitment made by Dr Tony Ma and Dr Prathima Chowdary, previous Fellows on the Endosurgical Unit.

Financial Support:
This project received financial support from the Norman Beischer Medical Research Foundation (NBMRF).

The authors have no financial interests to declare.

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Article type : Original Article

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Abstract

Background Persistent pelvic pain (PPP) remains an important cause of morbidity. Pelvic floor muscle spasm is an important contributor to PPP.

Aims The study's primary aim was to assess if Botulinum toxin (BoNT) injection to pelvic floor muscles altered pain scores or quality of life (QOL) at 6, 12 and 26weeks. Secondary

aims included investigating the impact of BoNT on opiate usage, examining the role of pain catastrophising, and assessing for complications.

Materials and Methods A single-centre prospective cohort study enrolled 21 patients with PPP who had failed physiotherapy techniques. Each participant underwent BoNT injection to muscles of the pelvic floor and pudendal nerve block. Questionnaires and digital vaginal examinations were conducted at baseline, 6, 12 and 26weeks. Pain score quantification used visual analogue scales (VAS) and numerical rating scales (NRS). Other outcome assessments included The World Health Organization Quality of Life instrument (WHOQOL-BREF), Pain Catastrophizing Scale (PCS), and modified Australian Pelvic Floor Questionnaire (AFPQ). ACTRN12620000067976.

Results Following BoNT injection, median VAS scores decreased for all domains at 6 and 12weeks, with VAS for dyspareunia significant at 6weeks($p=0.026$). Scores returned to baseline by 26weeks. Opiate usage was significantly less following BoNT injection, with a percentage reduction of 23.8% (95%CI -48.3 – 0.7, $p=0.06$). Sexual function improved significantly($p<0.01$), and at 6months, 4 previously apareunic participants reported successful penetrative vaginal intercourse. Health-related QOL and PCS demonstrated sustained improvement($p=0.02$-0.05). NRS for muscle tenderness decreased for all assessed muscle groups($p<0.001$).

Conclusions BoNT requires further assessment as a treatment modality for select women with PPP.

Introduction

Persistent pelvic pain (PPP) is a challenging clinical problem, and a major cause of morbidity and socioeconomic burden. PPP reduces work productivity by 45%, and increases absence from work by 15%.[1] Its exact prevalence is difficult to determine, however a recent systematic review by Ahangari (2014) estimated between 5.7% and 26.6%.[2] Unfortunately, a significant proportion of PPP remains inadequately managed.

There is increasing evidence that pelvic floor spasm is involved in up to 85% of PPP cases.[3,4] The exact relationship between muscle spasm and pain is not fully understood, but is thought to be secondary to compression of the muscle's blood supply leading to ischaemia, release of bradykinin and sensitization or excitation of nocioceptors.[5] Physical therapy aims to decrease

the resting tone of the muscles, and break the cycle of spasm and pain[6] however not all patients respond. Injection of Botulinum toxin (BoNT) into pelvic floor muscles is a novel treatment showing promising results in carefully selected women.[7,8-10]

BoNT acts by inhibiting the release of acetylcholine into the synaptic cleft at neuromuscular junctions, therefore inhibiting muscular contraction, decreasing pain associated with hypertonic muscles.[7] In 2015, Evans and Porter[11] describe BoNT injection into obturator internus (OI), bilaterally, and this study's intervention employs their technique.

The primary aim of our study was to assess whether BoNT injection alters pain scores or quality of life (QOL) at time points 6, 12 and 26weeks. Secondary aims included investigating the impact of BoNT injection on analgesia use and on sexual dysfunction, examining the associations between pain catastrophising and BoNT effectiveness, and assessing for complications.

Materials and Methods

Recruitment

A single-centre prospective cohort study enrolled 21 patients with PPP. Participants were recruited from endosurgical units at a tertiary centre in Melbourne (Australia) and from the private rooms of two study investigators (LE and ER). Inclusion criteria comprised female patients aged between 18-45years with PPP, who had previously undergone pelvic floor relaxation therapy with a specialist physiotherapist. Patients were excluded if they were pregnant, breastfeeding or planning a pregnancy during the study period, had a history of neuromuscular or bleeding disorder, or there was known hypersensitivity to BoNT.

Data collection and outcome measures:

Participants completed a baseline questionnaire detailing demographics, full medical and surgical history, and a visual analogue scale (VAS) assessing pelvic pain with separate scores for dysmenorrhoea, dyspareunia, dysuria, dyschezia and non-menstrual pelvic pain. Further assessment of how their pelvic pain affected their QOL, how they psychologically experienced their pain, and how it affected their other bodily functions was made using the following questionnaires: The World Health Organization Quality of Life instrument (WHOQOL-BREF)[12], The Pain Catastrophizing Scale (PCS)[13], and a modified Australian Pelvic Floor Questionnaire (AFPQ)[14,15]. Prior to BoNT injection, women underwent pelvic

floor digital muscle examination by one of the researchers (LE or ER). Participants rated their pain from 0-10 on a numerical rating scale (NRS) which was recorded on a standardised pain 'map' (Figure 1).

Botox administration

All procedures were performed in the operating theatre under general anaesthesia (without muscle relaxant) in the dorsal lithotomy position. 100units (Botox^{TM}, Allergan) in 15ml of 0.75% ropivacaine was injected into the pelvic floor muscles of each women, with ultrasound and nerve stimulator guidance as per the injection technique previously described.[11] The pain 'map' was used to decide on the division of the BoNT dose to each muscle. Following BoNT injection, a pudendal block was performed per vagina with 3-5 mL of 0.75% ropivacaine bilaterally to improve postoperative comfort.

Follow-up

Follow-up occurred at 6, 12, and 26weeks post BoNT injection. At these times, participants completed a questionnaire assessing pain scores (VAS), analgesia use, physiotherapy attendance, WHOQOL-BREF, PCS, and modified APFQ. A repeat pelvic floor digital muscle examination was performed and NRS recorded on the pain map.

Statistical Methods

Data was summarized as mean(SD), median(IQR) or number(%) depending upon type and distribution. Baseline patient characteristics and outcome measures at the four assessment times were summarized. For each outcome, analysis of change in mean scores over time was performed using non-linear cubic b-spline regression model with a robust variance estimate and the number of knots selected by cross validation. Sensitivity analysis was performed to assess whether there were differences in baseline characteristic dependent upon completion of 26week follow-up. Statistical analysis used Stata statistical software (StataCorp. 2019: Release 16. College Station, TX: USA). Significance level was set two-sided at 0.05 and was not adjusted for multiple comparisons.

This study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN:12620000067976). The study was approved by the Mercy Hospital for Women Human Research Ethics Committee (R15/54).

Results

Twenty-one participants were enrolled between March 2016 and November 2019. All participants completed the baseline questionnaire at recruitment and 19, 19, and 18 women completed the questionnaire at 6weeks, 3months and 6months respectively. Seventeen(81%) participants completed all 4 questionnaires. Baseline pelvic pain maps were available for all 21 participants. At 6weeks, 3months and 6months, completed pain maps were available for 18, 17 and 14 patients respectively. Fourteen(67%) participants had complete pain maps for all 4 time-points.

There were no differences between questionnaire responders and non-responders with regards to surgical history or opiate usage nor the year of BoNT administration. Responders at 26weeks were on average 6years younger than non-responders ($p=0.04$) and were more likely to be nulliparous ($p<0.001$). Responders also had reduced overall health QOL at baseline ($p=0.003$), and higher VAS for dyspareunia, dyschezia and dysuria ($p<0.001$). There were no differences in other pain scores or total PCS ($p>0.05$).

Demographics:

Baseline demographics are summarised in Table 1. Participant mean age was 32.9years. Thirteen patients had previously undergone laparoscopic pelvic surgery, with 7 having undergone multiple surgeries for pelvic pain. Six reported previous pregnancies, and 13 reported current hormonal menstrual suppression. All participants were regularly using analgesia. Seven were taking opiates daily, with the median morphine equivalent dose of 17.5mg per day (range 7.5mg–55mg/day). Fifteen participants were using regular neuroleptics (such as systemic amitriptyline and pregabalin). All participants reported current physiotherapy treatments.

Outcomes:

Study outcomes are presented in Table 2.

Pain scores:

Following administration of BoNT, there was an observed reduction in point estimate median pain scores for all domains at 6weeks and 12weeks. This was statistically significant for dyspareunia at 6weeks (p=0.026). VAS for all assessed pain domains returned to baseline by 26weeks (Table 2 and Figure 2a-e). At 26weeks, VAS were not different from baseline for dysmenorrhoea (p=0.57), other pelvic pain (p=0.47), dyspareunia (p=0.24), dyschezia (p=0.41) or dysuria (p=0.21).

Pelvic Floor Dysfunction Scores:

All 21 participants completed the Bowel Function and Bladder Function domains of the APFQ; two participants did not complete the Sexual Function domain. Mean(SD) baseline Bowel Function and Bladder Function scores (out of 36 and 42 respectively) were 9.8(7.2) and 7.9(6.5) respectively. Bowel and bladder function, as measured by the total APFQ score for these domains, did not alter over time (p= 0.74 and p=0.31 respectively).

Fourteen participants were apareunic at baseline, with 9(47%) participants citing 'Pain' to be the reason for avoiding penetrative vaginal intercourse. Twelve(63%) participants scored the maximum 19-points for dyspareunia. At 6months, of the 18 participants who completed the PFD questionnaire, 5(28%) remained apareunic due to pain. At all time points the total sexual dysfunction score was significantly reduced from baseline (p<0.01).

Quality of life:

The mean(SD) baseline scores (range 4-20) for the 4 domains – physical health, psychological health, social relationships, and environment – were 12.54(3.40), 13.44(3.23), 12.78(3.60), 16.2(2.55) respectively. The mean self-rated quality of life at baseline was 3.52(0.93) out of 5.0 and mean self-rated health satisfaction was 2.24(0.83) out of 5.0. For the Health domain alone, there was a 0.6 increase in mean score at 6weeks with the change maintained at the 12- and 26week assessments (p=0.03-0.05). There was no significant improvement in the remaining 5 of 6 aspects of the WHOQOL-Bref (p>0.10).

Pain catastrophising:

The mean(SD) PCS score at baseline was 24(10), with 8 patients scoring PCS>30, indicating that 38% of study participants scored in the clinically relevant 'high catastrophiser' range. Statistically significant reductions in mean PCS scores were found at 6weeks and sustained through to 26weeks for total PCS score (p=0.03-0.05), as well as PCS-rumination (p=0.02-

0.04) and PCS-helplessness (p=0.03-0.04). Interestingly, those with a baseline PCS >30 (n=8) demonstrated a similar reduction in total PCS when compared to those with a baseline PCS<30 (n=13). For both groups the mean total PCS score falls by -0.20 (95%CI -0.35, -0.05) per week or up to -5.2 (95%CI -9.1, -1.3) over the 6-month period.

A significant association was demonstrated between total baseline PCS and mean physical -0.24 (95%CI -0.45, -0.02, p=0.03) and psychological -0.26 (95%CI -0.49, -0.03, p=0.03) QOL score, with increasing PCS causing a significant reduction in both aspects of QOL at baseline.

Pelvic floor examination:

NRS on palpation decreased throughout the study period for all assessed muscle groups. Significant reductions in patient 'map' pain scores were observed over the 6month study period for right and left levator ani groups (p<0.001 and p<0.001 respectively), right and left obturator internus (p<0.003 and p<0.001 respectively), and superficial pelvic floor muscles (p=0.04). Vulval skin 'pain' sensation was also reduced (p=0.02).

Opiate Usage:

At baseline, 7 participants were taking regular opiates daily, with the median morphine equivalent dose of 17.5mg per day, range 7.5mg–55mg/day (Table 1). Over the 6month study period, 6 participants ceased their opiate usage, and one continued. An additional patient commenced opiates during the study period. This corresponds to an overall percentage decrease of -23.8% (95%CI -48.3 to 0.7, p=0.06) for opiate usage in the cohort.

Complications of treatment:

No serious complications occurred. Two participants reported weak legs for 6hours post injection, which resolved completely. It was hypothesised that this was a direct result of the pudendal nerve block, rather than the BoNT administration. No participant experienced urinary or faecal incontinence.

Discussion

Pelvic floor muscle spasm has been proposed as an important cause of PPP.[1] Botulinum toxin (BoNT) acts by inhibiting the release of acetylcholine into the synaptic cleft at neuromuscular junctions, therefore inhibiting muscular contraction, decreasing pain associated with muscle spasm.[7] The peak effect of BoNT is 2-5days, and lasts for 2-3 months.[7] BoNT has been used for different conditions since the 1990s including cervical dystonia, cerebral palsy and cosmetics, and more recently for other pain conditions such as migraine, painful bladder syndrome and facial pain syndromes.[16,17]

There are 2 types of gain that could be measured after BoNT injection: transient gain with one dose which may eventually wane, or a sustained gain. This study examines the transient gain with one dose. There are complex patient and systems implications associated with a medication that needs to be repeated to have a meaningful effect. If a true benefit of BoNT for pelvic pain is determined, then further studies are required to assess the longevity of single and repeat doses.

At the time of commencement, this study is the first prospective assessment of OI BoNT injection. Evans and Porter (2015) emphasise the importance of targeting obturator internus (OI) when utilising BoNT for the treatment of pelvic floor spasticity contributing to PPP.[11] With the nerve-stimulator localisation technique, the OI muscles were easily targeted. Interestingly, OI demonstrated the greatest improvement in tenderness assessment at 6months.

Our results demonstrate that 4 participants, previously apareunic due to pain, were able to commence penetrative sexual activity following BoNT injection. The validity of this finding is further supported by the sustained significant global reduction in tenderness found on vaginal examination at 6months. Important also is the complete cessation of regular opiate usage for 6 participants. In an era where opiate abuse constitutes an international medical emergency, treatments that offer an alternative to the dangers of opiates warrant close consideration.

While VAS for pelvic pain domains did not reveal significant sustained improvements (except for weak significance for dysuria) at 3months, the trends in VAS – dysmenorrhoea, other pelvic pain, and dyspareunia – demonstrate a possible improvement at the earlier time points. Significance was impacted by the small sample size. A recent double-blind placebo-

controlled study by Dessie et al (2019) demonstrated similar trends in reduced VAS at 4- and 12weeks when compared to placebo, but again failed to demonstrate significance.[18]

Our results demonstrate interesting findings for quality of life and pain catastrophisation. Over the study period, participants reported positive outcomes including sustained improvements in quality of life and health satisfaction, as well as reduced catastrophisation across 2 of 3 PCS domains. PCS reduced in a linear fashion following a similar slope regardless of baseline catastrophisation. Reduced psychological turmoil in response to pain is a crucially important outcome, however the uncontrolled study design renders it impossible to differentiate the effects of ongoing physiotherapy, increased clinical input, and the inherent validation of a patient's symptoms provided by the involvement in a novel treatment, from the effect of BoNT itself.

This study is limited by the lack of blinding in the assessment of pain and tenderness on vaginal examination. A pain map was used to objectively score the muscle groups, however at all follow-up visits both the patient reporting the tenderness and the clinician eliciting it were aware of the BoNT treatment. Moreover, aside from standardised pelvic examination, no other objective measure of pelvic floor spasm (eg monometry) was made upon enrolment or follow-up. We also did not control for alterations in analgesia over the study period, and thus do not know the impact of this on VAS outcomes and examination findings.

Unfortunately, the follow-up data was incomplete, although an acceptable response rate was gained for analysis. Follow-up questionnaire responders and non-responders demonstrated important differences in baseline QoL and pain VAS with those reporting worse QoL and higher pain scores being more likely to respond. This could have important implications in that it remains unknown how those less affected by their PPP symptoms respond to BoNT.

In keeping with the technique described by Evans and Porter (2015)[11] all patients received a pudendal nerve block. The block may reduce post-operative pain flare (nerve block lasts 6-8 hours) and the impact of the pudendal nerve block warrants future investigation; ideally with incorporation into a multi-arm randomised controlled trial (RCT).

Since Abbott et al (2006) published their RCT demonstrating promise for BoNT in the treatment for PPP, the literature has mainly comprised retrospective series and small

prospective cohorts.[9,19] Dessie et al (2019) published a recent RCT (double-blind placebo-controlled) comparing the efficacy of BoNT injection to saline but this study was primarily powered to assess treatment benefit at 2weeks and found no significant difference in pain outcomes.[18] RCTs to assess BoNT injection for PPP remain problematic. The ideal placebo control remains unknown. Saline injections are known to modify other pain responses, as is dry-needling. Additionally, optimal dosage, injection number and location, ideal BoNT-A compound, and contribution of pudendal nerve block require further prospective investigation.

It is hoped, that for well-selected patients, injection of pelvic floor muscles with BoNT offers an additional treatment to the currently inadequate clinical armoury. For several patients in our study, this treatment was transforming, particularly for those able to cease opiates and recommence penetrative intercourse. BoNT requires further examination as a treatment for select patients with PPP.

Figure Legends:

Figure 1: Standardised 'Pelvic Pain Map' prepared for study use. Numerical Rating Scales (NRS) for pain were obtained during digital vaginal examination and were annotated over muscle bulks to guide BoNT injection and offer an objective means of following clinical response following treatment.

Figure 2: Trends in Visual Analogue Scales (VAS) for 5 pain domains; (2a) Dysmenorrhoea, (2b) Dyspareunia, (2c) Non-menstrual pelvic pain, (2d) Dysuria, (2e) Dyschezia. Time point '6 weeks' demonstrated a statistically significant reduction in dyspareunia (p=0.026). At no other time point for any of the domains was the trend from baseline significant. VAS for all assessed pain domains returned to baseline by 26weeks.

Table 2: Data presented as median [25th to 75th percentile]

* except for dysmenorrhoea (≥13) as 8 or less women were functionally amenorrhoeic at time of completing the questionnaire; and dyspareunia (≥17) as 4 or less women were apareunic due to a non-pain related reason.

except for time point 26-weeks when ≥14

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Table 1. Participant Characteristics at Baseline	
	n = 21
Age (years), median (minimum, maximum)	32.49 (18.3, 51.0)
Age (years), mean (SD)	32.93 (9.83)
Previous pregnancy, n (%)	6 (28.6%)
Previous surgery for pain, n (%)	13 (61.9%)
Previous Surgery Type, n (%)	
Laparoscopy	12 (57.1%)
Laparotomy	1 (4.8%)
Previous Surgery Count	
Number, mean(SD)	3.46 (2.47)
Number, median (minimum, maximum)	3.00 (1.0, 9.0)
Medical Therapies	
Hormonal Suppression	
Yes, n(%)	13 (62.9%)
No, n(%)	8 (38.1%)
Opiate Use	
Yes, n(%)	7 (33.3%)
No, n(%)	14 (66.7%)
Opiate dose (mg morphine), median (minimum, maximum)	0.00 (0.0, 55.0)
Neuroleptic Use	
Yes, n(%)	15 (71.4%)
No, n(%)	6 (28.6%)
Sexual activity and symptoms	
Sexually active[#]	n = 19
Yes, n(%)	5 (26.3%)
No, n(%)	14 (73.7%)
Not sexually active due to pain, n(%)	9 (47.3%)

Table 2. Summary raw data at baseline at 6 ,12 and 26 weeks				
Time (weeks)	**0**	**6**	**12**	**26**
Pain VAS (number ≥19 at all assessments)*				
Dysmenorrhoea	7 [2 to 9]	3 [0 to 7]	6 [3 to 7]	7 [2 to 8]
Pelvic pain	8 [6 to 9]	7 [2 to 8]	6 [2 to 8]	6 [4 to 9]
Dysparunia	10 [8 to 10]	6 [3 to 10]	8 [4 to 10]	10 [4 to 10]
Dychezia	5 [1 to 8]	1 [0 to 6]	3 [0 to 6]	2 [0 to 6]
Dysuria	1 [0 to 7]	0 [0 to 2]	0 [0 to 4]	0 [0 to 4]
WHO QOL (number ≥19 at all assessments)				
Total	4 [3 to 4]	4 [3 to 4]	4 [4 to 4]	4 [4 to 4]
Health	2 [2 to 3]	3 [2 to 4]	3 [2 to 4]	3 [2 to 4]
Physical	12 [9 to 14]	14 [11 to 15]	14 [10 to 16]	14 [10 to 17]
Psychological	13 [13 to 14]	15 [12 to 15]	15 [12 to 16]	15 [13 to 16]
Social	12 [11 to 13]	13 [11 to 16]	14 [11 to 16]	15 [9 to 17]
Environmental	16 [15 to 17]	17 [15 to 18]	16 [14 to 18]	17 [15 to 19]
PCS (number ≥18 at all assessments)				
Total	24 [19 to 32]	15 [6 to 29]	14 [10 to 22]	18 [7 to 23]
Rumination	9 [7 to 12]	5 [3 to 9]	4 [3 to 9]	6 [3 to 9]
Magnification	3 [2 to 5]	2 [0 to 6]	2 [0 to 4]	3 [1 to 5]
Helplessness	13 [8 to 16]	8 [3 to 14]	8 [4 to 11]	7 [5 to 11]
PFD scores (number ≥18 at all assessments)				
Urinary	9 [3 to 12]	6 [2 to 12]	6 [3 to 11]	3 [2 to 9]
Bowel	9 [5 to 14]	10 [4 to 13]	8 [5 to 11]	9 [2 to 11]
Sex,	19 [11 to 19]	4 [0 to 11]	8 [2 to 19]	7 [1 to 12]
Pelvic Muscle Map scores (number ≥17 at all assessments)#				
LAR	6 [4 to 7]	2 [1 to 3]	2 [0 to 2]	4 [3 to 5]
LAL	6 [4 to 8]	2 [1 to 5]	2 [0 to 3]	4 [3 to 5]
OAR	7 [5 to 9]	1 [0 to 4]	2 [0 to 3]	4 [1 to 5]
Superficial	4 [0 to 5]	1 [0 to 4]	0 [0 to 2]	2 [0 to 3]

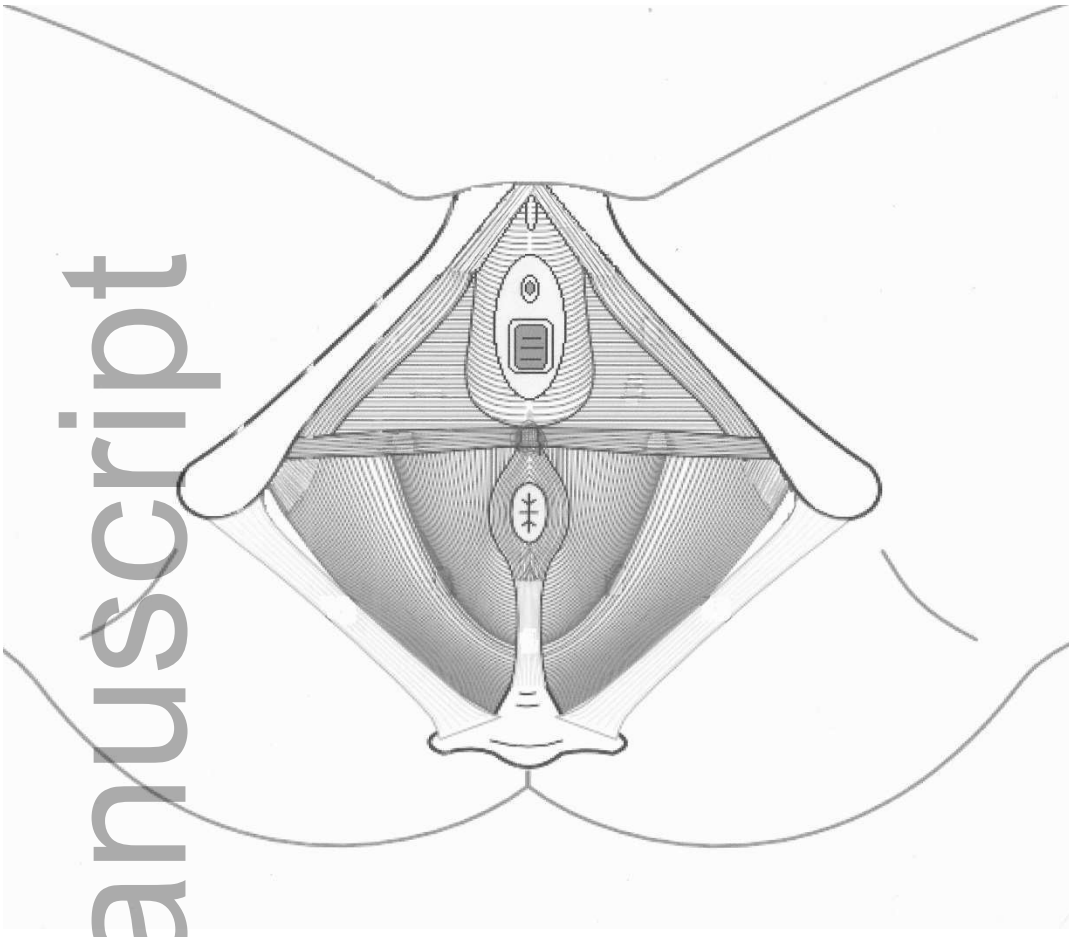
Data presented as median [25th to 75th percentile]

* except for dysmenorrhoea (≥13) as 8 or less women were functionally amenorrhoeic at time of completing the questionnaire; and dyspareunia (≥17) as 4 or less women were apareunic due to a non-pain related reason.

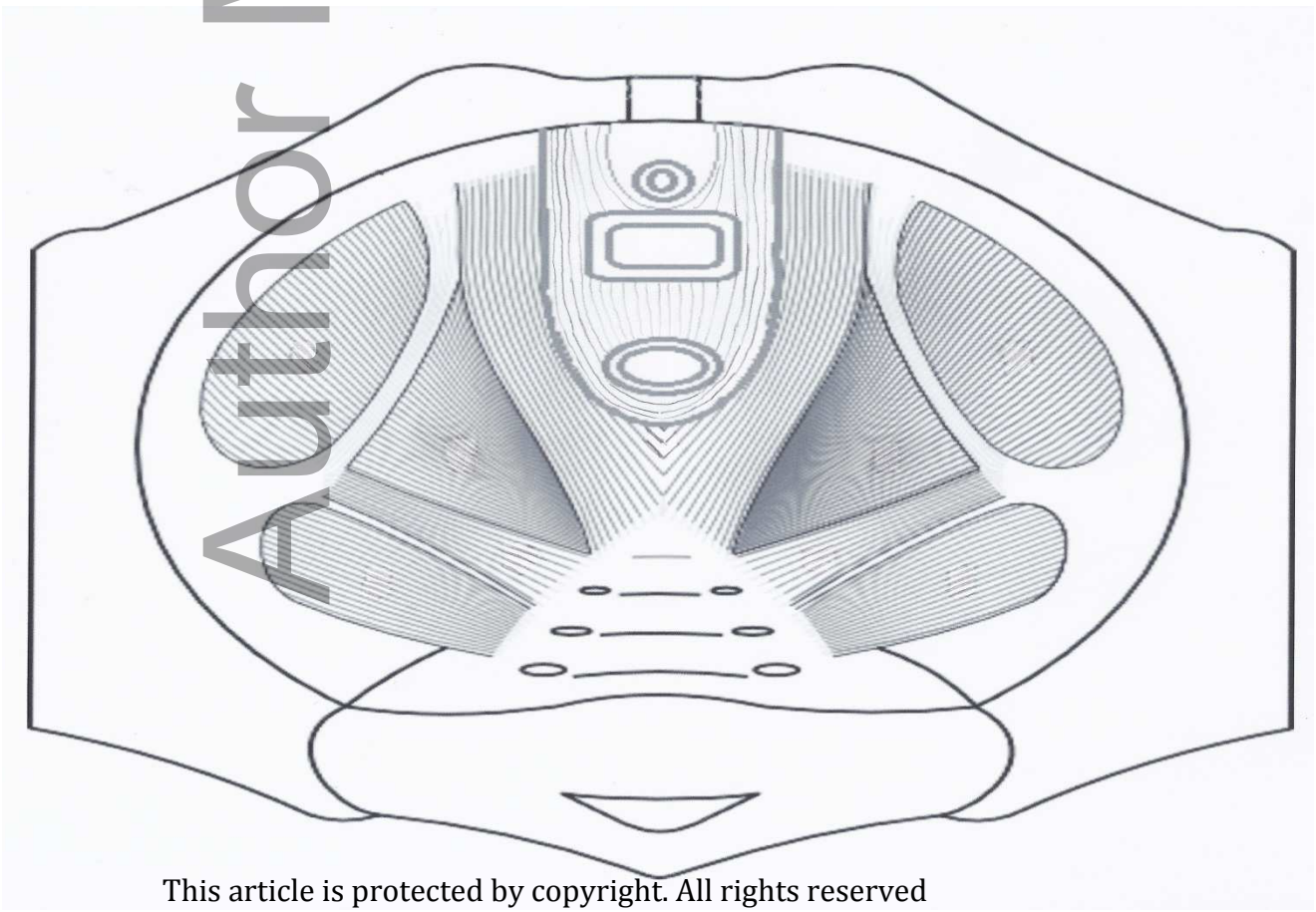
except for time point 26-weeks when ≥14

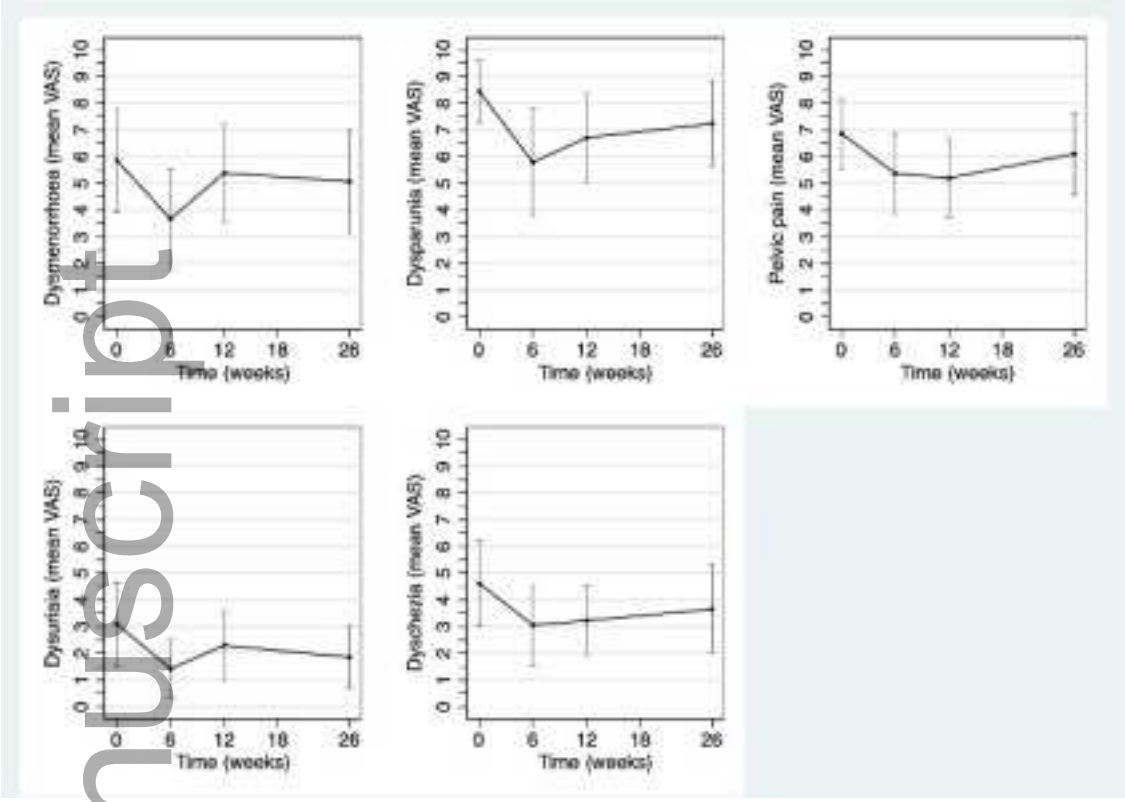
PAIN MAP

Superficial



Deep





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