

## The effects of a range of treatment modalities on pain symptoms and overall health in women attending an endometriosis clinic

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### Abstract

#### *Aims*

Treatments for endometriosis include conservative, medical and surgical treatments. There is no definitive evidence to support one intervention over another. Women attending an endometriosis clinic will use various treatment modalities over time, depending on the success of each and the ability to achieve pregnancy when desired.

This study seeks to examine the change in symptomatology and overall health score in response to various treatment interventions applied across many patients over a prolonged timeframe to examine the effectiveness of various treatments in women with endometriosis.

#### *Methods*

This was a longitudinal prospective cohort study performed in a tertiary gynaecology centre in Cork University Maternity Hospital, Ireland. Data for the study, in the form of patient-completed questionnaires, were prospectively collected from May 2012 to February 2020 and analysed by the authors between April and June 2020.

#### *Results*

Four hundred and twenty-eight questionnaires were analysed. Data was available for 162 women. The study demonstrated significant reduction in premenstrual pain, dysmenorrhoea, postmenstrual pain, midcycle pain, dyschezia and dyspareunia.

#### *Discussion*

We observed a significant improvement in most patient-reported pain symptoms over time with the use of a range of treatment interventions for endometriosis, supporting current practices in our endometriosis clinic.

## Introduction

Endometriosis frequently presents with premenstrual pain, dysmenorrhoea, and dyspareunia. The objectives of treatment for endometriosis are the management of pain symptoms and prevention of disease progression, whilst respecting the patient's desire to achieve pregnancy. Analgesic agents such as paracetamol, ibuprofen and mefenamic acid are commonly used first-line for the treatment of dysmenorrhoea. Combined hormonal contraceptive agents, in addition to relieving pain, offer the advantage of providing contraceptive protection and menstrual cycle control, and long-term safety data exists for these treatments<sup>1</sup>. Progestogens such as medroxyprogesterone or the levonorgestrel-releasing intrauterine system (LNG-IUS) can be used to reduce endometriosis-associated pain<sup>2</sup>. Gonadotrophin releasing hormone analogues (GnRHa) use induces amenorrhoea thus improving dysmenorrhoea<sup>3</sup>. Surgical intervention for endometriosis has been demonstrated to be effective in reducing pain and improving quality of life (QoL)<sup>4</sup>. Treatment modalities often change over the course of a woman's reproductive life, depending on her fertility wishes and response to different treatments. Management may be multimodal, with a combination of treatment modalities being used to treat overlapping pain syndromes as well as endometriosis. This study seeks to examine the change in symptomatology and overall health score in response to various treatment interventions, to examine the effectiveness of various treatments in women with endometriosis.

## Methods

### *Study Design*

A prospective cohort study of women attending the endometriosis clinic at Cork University Maternity Hospital (CUMH). Data was collected from May 2012 to February 2020.

### *Participants*

Patients referred to the endometriosis clinic at CUMH are required to either have a prior laparoscopic diagnosis of endometriosis, convincing clinical evidence of endometriosis, or convincing radiological evidence of endometriosis. Patients were requested to complete a questionnaire at each visit to the endometriosis clinic during the study period.

### *Procedure*

Data for the study were collected in patient-completed questionnaires. At each visit patients were asked to report current symptoms and pain scores as well as overall health score. The quantitative data on patients' symptoms regarding pain scores and overall health related to treatment modality are addressed in this paper.

### *Survey and measures*

Patients were asked to score their pain in the following domains: mid-cycle pain, premenstrual pain, dysmenorrhoea, postmenstrual pain, dyschezia, dyspareunia and dysuria. Patients were asked to rate their pain in each domain using a score from 0 to 10, where 0 describes no pain and 10 the worst pain imaginable. In addition, patients were asked to record their overall health on a scale of 0-100 where 0 describes the worst health and 100 the best health.

Treatment modalities used in the interval between clinic visits were recorded at each visit. Non-hormonal treatments included paracetamol and/or other non-steroidal anti-inflammatory drugs (NSAIDs). Hormonal treatments included combined (COCP) or progesterone only (POP), depot medroxyprogesterone acetate (DMPA). LNG-IUS treatment, although a hormonal treatment, was assessed separately as it does not suppress ovulation. GnRHa treatment, although a hormonal treatment, was assessed separately as it results in a profound hypo-estrogenic state. Surgical treatments included any surgical intervention, to include laparoscopic excision or ablation of endometriosis, oophorectomy, or hysterectomy. Gastro-intestinal agents included laxatives or antispasmodic use. Physiotherapy treatment included any intervention used for the treatment of pelvic pain or other musculoskeletal contributors to pain. Treatment interventions were confirmed by reviewing doctors' letters dictated at the time of the clinic.

### *Statistical analysis of data*

Data were transcribed to Excel and analysed using STATA V12<sup>5</sup> and SPSS V 25<sup>6</sup>. Descriptive analysis for pain scores and overall health scores were conducted using means and 95% confidence intervals to compare scores from baseline and follow-up. Linear mixed-effects regression models were used to estimate the effects of treatment, and of changes over time on mean pain scores and QoL.

## **Results**

Data was available for 162 women. Baseline data were available for 106 women. There were 56 women who had data recorded for at least one follow-up visit but whose baseline questionnaire was not available for analysis. The mean number of clinic visits per patient during the study period was 2.6. Baseline visit to 5<sup>th</sup> follow-up clinic was recorded in 17 cases. Four hundred and twenty-eight questionnaires were analysed. These comprised 106 first visit and 322 follow-up questionnaires over the course of between one and five follow-up clinic attendances.

Table 1 shows the effect of treatment modalities on patient symptoms and overall health according to various treatment interventions. It also shows the change in symptoms and overall health over the course of attendances at follow-up clinic visits.

Table 1: Effects of treatment interventions and time on patient pain scores and overall health

	Mid-cycle pain	Premenstrual pain	Dysmenorrhoea	Postmenstrual pain	Dyschezia	Dyspareunia	Dysuria	Overall Health
<b>No (%) with symptom at 1<sup>st</sup> visit</b>	66 (62.3)	82 (77.4)	93 (87.7)	61 (57.5)	64 (60.4)	67 (63.2)	27 (25.5)	NA
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
<b>Baseline pain score (range)</b>	4.4 (3.3, 5.4)	6.5 (5.4, 7.6)	8.2 (7.1, 9.3)	3.6 (2.7, 4.6)	4.3 (3.2, 5.4)	5.0 (3.8, 6.2)	1.6 (0.8, 2.4)	66.7 (59.8, 73.5)
<b>TREATMENT EFFECT</b>								
<b>Treatment (% in whom treatment used at any time during study period)</b>								
<b>Non-hormonal (59.3)</b>	0.2 (-0.4, 0.9)	0.1 (-0.6, 0.8)	0.6 (-0.2, 1.3)	1.0 (0.4, 1.6)**	0.5 (-0.2, 1.1)	0.6 (0.0, 1.2)	0.6 (0.1, 1.1)*	-5.8 (-10.0, -1.6)**
<b>Hormonal (65.4)</b>	-0.3 (-0.9, 0.3)	-0.8 (-1.4, -0.1)*	-1 (-1.7, -0.3)**	0.1 (-0.5, 0.7)	-0.6 (-1.2, 0.0)	-0.4 (-1.0, 0.2)	-0.3 (-0.7, 0.2)	2.6 (-1.3, 6.5)
<b>Surgical (27.8)</b>	-0.3 (-1.2, 0.5)	-0.9 (-1.8, 0.0)*	-1.4 (-2.3, -0.4)**	-0.7 (-1.5, 0.2)	-1.1 (-2.0, -0.3)	-0.5 (-1.3, 0.3)	-0.1 (-0.7, 0.6)	0.2 (-5.3, 5.8)
<b>GnRHa treatment (23.5)</b>	-1.3 (-2.2, -0.5)**	-1.6 (-2.5, -0.7)**	-1.9 (-2.8, -0.9)***	-0.1 (-0.9, 0.8)	-0.3 (-1.2, 0.6)	-0.5 (-1.4, 0.4)	0.2 (-0.4, 0.8)	-1.9 (-7.5, 3.7)
<b>IUS (14.8)</b>	-1.3 (-2.4, -0.1)*	-0.3 (-1.5, 0.9)	-0.9 (-2.1, 0.3)	-1.2 (-2.3, -0.2)*	0.0 (-1.2, 1.2)	-0.2 (-1.5, 1.1)	-0.5 (-1.3, 0.4)	3.2 (-4.2, 10.6)

<b>Bowel agents (29.0)</b>	-0.5 (-1.3, 0.3)	-0.4 (-1.2, 0.5)	-0.6 (-1.5, 0.3)	0.1 (-0.7, 0.9)	0.9 (0, 1.7)*	-0.2 (-1.0, 0.6)	-0.1 (-0.7, 0.5)	-4.2 (-9.6, 1.2)
<b>Physio (13.6)</b>	-0.5 (-1.6, 0.7)	-0.7 (-1.9, 0.5)	-0.7 (-2.0, 0.6)	-1.0 (-2.1, 0.1)	-0.1 (-1.2, 1.1)	-0.2 (-1.3, 1.0)	-0.1 (-0.9, 0.8)	1.7 (-5.7, 9.1)
<b>TIME EFFECT</b>								
<b>1<sup>st</sup> follow-up</b>	-0.4 (-1.1, 0.3)	-0.9 (-1.7, -0.1)*	-0.9 (-1.8, -0.1)*	-1.1 (-1.8, -0.3)**	-0.2 (-1.0, 0.5)	-0.6 (-1.3, 0.1)	-0.5 (-1.0, 0.0)	-1.4 (-6.1, 3.3)
<b>2<sup>nd</sup></b>	-0.9 (-1.7, 0.0)*	-1.4 (-2.3, -0.5)**	-1.2 (-2.2, -0.2)*	-1.7 (-2.6, -0.9)***	-1.5 (-2.3, -0.6)***	-0.9 (-1.7, -0.1)*	-0.6 (-1.2, 0.0)	3.1 (-2.4, 8.5)
<b>3<sup>rd</sup></b>	-0.4 (-1.3, 0.6)	-0.7 (-1.7, 0.3)	-1.4 (-2.5, -0.3)*	-1.7 (-2.7, -0.7)**	-1.0 (-2.0, 0.0)*	-0.8 (-1.7, 0.2)	-0.2 (-0.8, 0.5)	-3.1 (-9.3, 3.1)
<b>4<sup>th</sup></b>	-1.1 (-2.2, 0.1)	-1 (-2.2, 0.2)	-1.8 (-3.1, -0.5)**	-1.4 (-2.5, -0.3)*	-1.3 (-2.4, -0.1)*	-1.3 (-2.3, -0.2)*	-0.5 (-1.3, 0.3)	-1.1 (-8.3, 6.1)
<b>5<sup>th</sup></b>	-2.4(-3.8, -0.9)***	-3.3(-4.8, -1.7)***	-4.2(-5.9, -2.5)***	-2.6 (-4.1, -1.2)***	-1.9 (-3.3, -0.4)*	-1.6 (-2.9, -0.2)*	0.1 (-0.9, 1.1)	-1.6 (-11.1, 7.8)

Note; analysis also adjusted for age effects; CI=confidence interval; \*p-value <0.05, \*\*p-value <0.01, \*\*\*p-value<0.001

### *Premenstrual pain*

This symptom was reported by 77% of patients at their baseline clinic visit with a mean pain score of 6.5. Over the course of treatment at the endometriosis clinic, use of hormonal treatment, GnRHa and surgery resulted in a significant improvement in premenstrual pain.

### *Dysmenorrhea*

Dysmenorrhea was reported by 88% of patients at baseline visit. Mean baseline pain score at first visit was 8.2, reducing with each consecutive clinic visit. The treatment modalities which led to a significant reduction in dysmenorrhea pain score were hormonal treatment, surgical management and GnRH agonist use.

### *Postmenstrual pain*

Postmenstrual pain was reported by 57.5% of patients at baseline visit, with a mean pain score of 3.6. These scores improved at the first return visit and remained reduced with each subsequent visit. The treatment most effective for reducing postmenstrual pain was the use of LNG-IUS.

### *Mid-cycle pain*

Mid-cycle pain was reported by 62% of patients at baseline visit with a mean pain score of 4.4. There was an improvement in this symptom over time; we observed significant improvement with the use of GnRH agonist and LNG-IUS.

### *Dyschezia*

Dyschezia was reported by 60% of patients at baseline visit with a mean pain score of 4.3. This symptom improved significantly following surgical treatment and showed sustained improvement over the course of follow-up. We observed a deterioration in dyschezia score with the use of antispasmodic / laxative treatment in our population.

### *Dyspareunia*

Dyspareunia was reported by 63% of women at baseline visit with a mean pain score of 5.0. We did not observe an improvement in scores with any specific treatment modality. There was an improvement in patient reported dyspareunia severity over the course of multiple attendances at clinic.

### *Dysuria*

This symptom was reported by 25.5% of patients at baseline visit, with a mean pain score of 1.6. There was no change in this score over the course of follow-up visits.

### *Overall health*

Mean health score at first visit was 66.7. This did not change significantly with any treatment modality, nor did it improve over time. We observed lower overall health score by the fifth return visit. A deterioration in overall health score was found with the use of non-hormonal treatment.

## Discussion

We observed improvements in most patient-reported pain symptoms over time with the use of a range of treatment interventions for endometriosis.

### *Non-hormonal treatment*

Used by 60% of patients during their treatment course, non-hormonal treatment was not associated with a significant improvement in pain scores. There was a worsening of postmenstrual pain and dysuria, as well as a decrease in overall health score. Our findings concur with a the lack of high-quality evidence indicating benefit of NSAIDs in patients with endometriosis-related pain<sup>7</sup>.

### *Levonorgestrel releasing Intrauterine system (LNG-IUS)*

Use of the LNG-IUS in 15% of patients had no significant effect on dysmenorrhea although an improvement was observed in midcycle and postmenstrual pain. Recent guidance from the European Society for Human Reproduction and Endocrinology (ESHRE) recommends LNG-IUS use to manage endometriosis-related pain<sup>8</sup>. However the World Endometriosis Society (WES) Consensus on the Current Management of Endometriosis states that more data is needed on the relative effectiveness of LNG-IUS treatment and suggest its use as a second line agent<sup>9</sup>.

### *Hormonal treatment*

Used in 65.4% of patients during the study period, hormonal treatment had a significantly beneficial effect on premenstrual pain and dysmenorrhoea.

Our findings indicate a beneficial effect of COCP use in endometriosis-related pain and support our current practice of first-line use of hormonal treatment in women with presumed or diagnosed endometriosis who are not actively trying to conceive. This practice is in line with research demonstrating that COCP reduces dyspareunia, dysmenorrhoea and non-menstrual pain, and is endorsed by both ESHRE and WES guidance on the management of endometriosis<sup>8,9</sup>. A meta-analysis examining endometrioma recurrence post-operatively found that long-term use of an oral contraceptive was protective<sup>10</sup>.



### *GnRH agonist treatment*

Around a quarter (23.5%) of our patient cohort had GnRHa treatment during the study period. This resulted in the greatest reduction in mean pain score between assessments. There were reductions in mid-cycle and premenstrual pain as well as dysmenorrhoea. These findings are consistent with those of a 2010 Cochrane review which concluded that GnRHa was more effective than placebo in relieving endometriosis-associated pain<sup>11</sup>.

Whilst providing good symptom relief in our patient cohort, its use is limited to 24 months in our service, with subsequent stepdown to a hormonal agent being the usual practice.

### *Surgical treatment*

Over a quarter (27.8%) of patients attending the endometriosis clinic underwent surgical treatment during the study period. Excision of endometriosis was the predominant surgical approach in our service, although some patients underwent hysterectomy and /or oophorectomy. We observed an improvement in premenstrual pain ( $p<0.05$ ), dysmenorrhoea ( $p<0.01$ ) and dyschezia ( $p<0.05$ ) following surgical intervention. These findings are consistent with previously published literature<sup>12</sup>.

### *Laxative / antispasmodic treatment*

Medication to assist bowel function or to relieve bowel-related pain were used in 30% of patients. We observed a worsening of dyschezia with these treatments. Constipation and IBS frequently present as overlapping pain syndromes in women with endometriosis. Jaiwala et al have suggested that smooth-muscle relaxants such as mebeverine hydrochloride are beneficial in the treatment of IBS where abdominal pain is a prominent feature<sup>13</sup>.

### *Physiotherapy*

Physiotherapy referral was made for 14% of patients in our group. Myofascial pelvic pain (MPP) is commonly encountered in patients with endometriosis and chronic pelvic pain, for which physiotherapy treatments are usually beneficial. One would expect an improvement in the symptom of dyspareunia in women with MPP referred for physiotherapy. The waiting time for physiotherapy assessment and treatment was very long in our unit during the study period. Duration of treatment for MPP is variable among patients, depending on the degree of pelvic floor hypertonicity. These factors may have had an impact on the results for this treatment modality.

### *Overall Health Score*

Overall health score did not show improvement with the different treatment interventions or over multiple visits to the endometriosis clinic. This might be explained by the fact that

patients who respond to treatment are discharged once sustained symptom control is confirmed. This typically occurs after a 12–24-month follow-up period.

In contrast, patients whose symptoms are less well controlled continue to attend the clinic, reporting lower overall health scores. Patients not responding so well to treatments and those refractory to usual treatments tend to have a more prolonged treatment course and return lower overall health scores.

### *Study limitations*

A large group of patients did not have data available from the first visit questionnaire. However, valid information regarding the treatment effect of the most recently-applied intervention could still be obtained for all patients having more than one clinic visit.

This was a pragmatic longitudinal observational study of a large group of patients. Thus, an average change in pain scores and overall health according to treatment type was calculated, rather than individual patients' responses to subsequent treatment modalities. However, as data was linked to the patient record number it may be possible to re-interrogate the data via another study to report more individualised longitudinal information.

Due to the questionnaire format of the study it is unfortunately not possible to provide specific information on how many patients were discharged from the clinic during the study period.

There is a possibility of skewing in our data in relation to some follow-up scores. Treatment effect was gauged on the most recently-applied intervention, and multimodal treatment was used in many cases. The treatment effect of surgery for example, may have been affected by the concomitant use of hormonal treatment after surgery which we usually recommend to reduce the likelihood of disease recurrence in women not trying to conceive or have had tolerance issues. However, the decision to proceed to surgery is often made on the basis of failure of medical treatment to control symptoms, and thus a majority patients are have been using hormonal treatment pre-operatively.

Our study demonstrated an improvement in most pain types over time in women attending the endometriosis clinic in our unit, but not changes were demonstrated in the overall health score. The treatments found to be most beneficial for premenstrual pain and dysmenorrhea, the cardinal symptoms of endometriosis and those associated with the highest pain scores at first presentation, were GnRHa, surgery and hormonal treatment.

### **Declarations of Conflicts of Interest:**

None declared.

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