

# **Laparoscopic ablation or excision with helium thermal coagulator versus electrodiathermy for the treatment of mild-to-moderate endometriosis: randomized controlled trial**

Short title: Laparoscopic treatment of endometriosis

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# **Laparoscopic ablation or excision with helium thermal coagulator versus electrodiathermy for the treatment of mild-to-moderate endometriosis: randomized controlled trial**

## **Abstract**

**Objective:** To compare electrodiathermy with helium thermal coagulation in laparoscopic treatment of mild-to-moderate endometriosis.

**Design:** Parallel-group randomized controlled trial.

**Setting:** A UK endometriosis centre.

**Population:** Non-pregnant women aged 16–50 with a clinical diagnosis of mild-to-moderate endometriosis.

**Methods:** If mild or moderate endometriosis was confirmed at laparoscopy, women were randomized to laparoscopic treatment with electrodiathermy or helium thermal coagulator.

**Main outcome measures:** Cyclical pain and dyspareunia (rated on 100mm visual analogue scales), and quality of life, at baseline, 6, 12, and 36 weeks following surgery; operative blood loss; surgical complications.

**Results:** 192 women were randomized. 155 (81%) completed the primary outcome point at 12 weeks. In an intention-to-treat analysis, VAS scores for cyclical pain were significantly lower in the electrodiathermy group compared to the helium group at 12 weeks (mean difference = 9.43mm; 95% CI = 0.46, 18.40;  $p = 0.039$ ) and across all timepoints (mean difference = 10.13mm; 95% CI = 3.48, 16.78;  $p = 0.003$ ). A significant difference in dyspareunia also favoured electrodiathermy at 12 weeks (mean difference = 11.66mm; 95% CI

1.39, 21.93;  $p = 0.026$ ). These effects were, however, smaller than the proposed minimum important difference of 18.00mm. Differences in some aspects of quality of life favoured electrodiathermy. There was no significant difference in operative blood loss (fold-change with helium as reference = 1.43; 95% CI 0.96, 2.15;  $p = 0.081$ ).

**Conclusions:** Although electrodiathermy was statistically superior to helium ablation in reducing cyclical pain and dyspareunia, these effects may be too small to be clinically significant.

**Funding:** This study was funded by the National Institute for Health Research under its Research for Patient Benefit Programme (project number PB-PG-0212-27072).

**Trial registration:** ISRCTN 50928834

**Keywords:** endometriosis, laparoscopic surgery, pelvic pain

**Tweetable abstract:** Helium coagulation is not superior to electrodiathermy in laparoscopic treatment of mild-to-moderate endometriosis

## INTRODUCTION

Endometriosis is described as the presence of endometrium or endometrium-like tissue at sites other than the uterine cavity.<sup>1</sup> This chronic and benign gynaecological condition has a prevalence of approximately 5%–10% in women of reproductive age, increasing to 30%–50% in cases of infertility.<sup>1,2</sup> Prevalence peaks between 25 and 35 years of age.<sup>1</sup> Symptoms include abdominopelvic pain, dyspareunia and infertility,<sup>3</sup> all of which can decrease quality of life.<sup>4</sup>

Endometriosis is challenging to treat owing to the chronic and recurrent nature of the symptoms, whose severity does not correlate with the extent of disease visualized at laparoscopy – the gold standard for diagnosis.<sup>3</sup> There is frequently significant delay from onset of symptoms to final diagnosis, leading to further morbidity.<sup>5</sup> The problem is compounded by a lack of objectivity in assessing clinical features, relying upon subjective perception of pain severity, which shows inter-individual variation.

Treatment aims for endometriosis include relieving pain and improving fertility. Analgesia, with or without hormonal therapies, may be used on an empirical basis before a formal diagnosis is made.<sup>6</sup> If symptoms persist despite medical treatment, a “see-and-treat” approach may be undertaken whereby endometriosis is treated with excision and/or ablation at initial diagnostic laparoscopy.<sup>6</sup>

A meta-analysis has demonstrated that laparoscopic surgery can improve symptoms of endometriosis.<sup>7</sup> Typically, treatment of endometriosis is with electrodiathermy; however, there are limitations as to where electrodiathermy can be safely used, for example when close to the bowel or bladder. An alternative procedure, the helium thermal coagulator, uses a combination of helium gas and very low electrical power (2–8 watts) to deliver an inert plasma of gas to the affected tissue. The probe is directed laparoscopically to the affected area and has no physical contact with the tissue when activated. Careful control of power levels allows extremely precise degrees of cauterization to be applied. Because the interaction between electrons and tissue occurs in helium, no smoke is generated. Low thermal spread potentially allows safe ablation of endometriosis over usually inoperable areas that may be injured with the increased penetration of electrodiathermy, such as tissue overlying the bladder, bowel and diaphragm. NICE cites evidence relating to the safety of the technique from case series but recognizes a lack of evidence relating to efficacy.<sup>8</sup>

The objective of this study was to determine whether laparoscopic treatment of mild-to-moderate endometriosis with a helium thermal coagulator is associated with superior symptom relief and reduced morbidity compared to treatment with electrodiathermy.

## **METHODS**

We conducted a randomized parallel-group controlled trial, with equal allocation, in which patients with mild-to-moderate endometriosis underwent laparoscopic excision and/or ablation of endometriosis with either helium thermal coagulator or hook electrodiathermy.

### **Participants and recruitment**

Women between the ages of 16 and 50 presenting between January 2014 and September 2017 to a UK gynaecology outpatient clinic with pelvic pain and a clinical diagnosis of mild or moderate endometriosis were offered recruitment into the trial following a full explanation. We excluded those with the possibility of a gynaecological cancer, or who had advanced endometriosis, or who were currently pregnant. The patient then gave written consent and baseline data on outcome measures were recorded prior to surgery. A translator was provided where necessary.

### **Sample size**

To detect a 12-week mean difference in VAS scores for cyclical pain of 18mm with a standard deviation (SD) of 40mm (assuming equal allocation, 80% power and a 5% two-tailed significance level), data from a minimum of 79 women in each arm were required. Assuming a maximum of 15% loss to follow-up, at least 93 women needed to be recruited to each arm. The SD was set at the highest relevant estimate found in the literature,<sup>9-12</sup> and 18mm was taken as the minimum important between-group difference (MID) based on information from this literature.<sup>11</sup>

## **Randomization**

Participants were randomized to laparoscopic ablation and/or excision with either helium thermal coagulator or electrodiathermy. A randomization list, using random permuted blocks of sizes between 2 and 8, was drawn up by an independent statistician and incorporated in a password-protected database constructed by an information technology specialist who had no other role in the study.

## **Blinding**

The study was double-blinded, whereby participants, assessors and the trial statistician were not aware of the intervention received. Of necessity, the surgeon was not blind to the intervention. Since both groups of patients had laparoscopic treatment, there were no indicators to the patients, nursing staff or other clinicians to suggest which intervention had been performed. Post-operative management did not indicate to the women the procedure received, and steps were taken to ensure that this was not revealed by their treating surgeon during post-operative recovery prior to discharge (4 hours approximately). An emergency unblinding procedure was in place in the event of readmission with significant postoperative complications.

## **Procedure**

Laparoscopy was performed to either confirm or exclude the diagnosis of endometriosis. If endometriosis was present, staging using the Revised American Society for Reproductive Medicine (RASRM) classification of

endometriosis<sup>13</sup> was carried out. If no endometriosis was present, or the extent of disease was greater than mild-to-moderate, the patient was not randomized and was excluded from the trial. In cases where endometriosis was confirmed, the surgeon then logged into the randomization database and was provided with the code for the procedure to be performed (helium thermal coagulator or hook electrodiathermy). In relation to both procedures, the surgeon performed ablation and/or excision, depending upon clinical judgment as to the severity and depth of disease and with regard to delicate underlying structures. Intraoperative blood loss and any complications were recorded. The patient was discharged home after approximately 4 hours.

#### **Data collection and outcome measures**

Although currently in development,<sup>14</sup> no core outcome set for endometriosis was available to guide the selection of outcome measures. Baseline data on demographics, clinical history and outcome measures were collected prior to surgery. The primary outcome measure was cyclical pain. Secondary outcome measures were dyspareunia, quality of life, operative duration, intraoperative blood loss, intraoperative visceral complications, post-operative complications, and conception rates among those seeking to become pregnant.

Participants were invited to attend a dedicated outpatient follow-up clinic to be assessed by an independent practitioner (research nurse), blind to the procedure the patient had received. Clinics were conducted at 6, 12, and 36 weeks following surgery. At each visit an assessment of the worst intensity of



both cyclical pain and dyspareunia, over the previous four weeks, was performed using 100mm visual analogue scales, which are commonly used for endometriosis-related symptoms.<sup>1,9,10,12,15,16</sup> Quality of life was also assessed at these time-points using the Endometriosis Health Profile (EHP-30) questionnaire.<sup>17,18</sup> This measure has five 0–100 subscales: pain, control and powerlessness, emotional well-being, social support, and self-image. Lower scores indicate better quality of life.

Post-operative complications were assessed at the 6- and 12-week timepoints. Any participant who successfully conceived, or attempted to do so, during the 36-week follow up was also noted. Women failing to attend follow-up were sent a self-assessment form on the primary outcome (cyclical pain intensity at 12 weeks) and asked to return this by post.

### **Statistical analysis**

Data analysis was blind to group allocation on an intention-to-treat basis. The primary outcome, between-group differences in VAS scores for cyclical pain, was analysed at 12 weeks and also across the full follow-up period, with a linear mixed model (with repeated observations clustered within participants); using maximum likelihood estimation, and assuming that values are missing at random, this analysis accommodates missing data and thus includes all randomized participants.<sup>19</sup> Covariates in the model, selected *a priori*, were baseline VAS scores, age, surgeon (surgeon A, surgeon B), staging on the RASRM classification (mild, moderate, severe) and history of previous pelvic surgery (yes, no). For secondary outcomes, a similar analysis was performed.

Pregnancy rates were compared using logistic regression, with maximum likelihood estimation. A secondary unadjusted analysis was performed on the primary outcome measure, but an intended per protocol sensitivity analysis<sup>20</sup> was not performed, as all but one participant received the randomized intervention. Statistical significance was set at  $p \leq 0.05$  (two-tailed) and 95% confidence intervals (CIs) were calculated for all estimates. Assumptions of all statistical models were checked and data were analysed in IBM SPSS version 25.

### **Patient involvement**

We held a focus group of patients prior to the study to explore the perceived importance of the research, the procedures to be tested, the choice of outcome measures, and the timing of their administration. The views expressed in the focus group informed the design of these aspects of the study. Two patient representatives were co-applicants on the funding proposal and subsequently became members of the trial steering committee, and these and one other patient representative reviewed the paper prior to submission.

### **Funding**

This study was funded by the National Institute for Health Research under its Research for Patient Benefit Programme (project number PB-PG-0212-27072).

## RESULTS

One hundred and ninety-two women were randomized to the two interventions between January 2014 and September 2017. In total, 274 women were excluded from the study, of whom 106 were rejected once in theatre, predominantly because no endometriosis was identified at laparoscopy. Baseline characteristics of randomized participants are shown in Table 1; variables were well balanced across the trial arms. Progress through the trial is shown in the CONSORT diagram (Figure 1). There was one protocol deviation: a woman randomized to treatment with electrodiathermy received treatment with a helium thermal coagulator.

Among participants treated with helium thermal coagulator, ablation was performed on 36 (40%), excision was performed on 7 (8%), and 47 (52%) received both ablation and excision. The corresponding figures for electrodiathermy were 1 (1%), 20 (21%) and 73 (78%). Information was missing in respect of 8 participants.

Table 2 shows values of outcome variables at follow-up. For the primary outcome of cyclical pain, at 12-week follow-up the covariate-adjusted VAS scores were significantly lower in the electrodiathermy group compared with the helium group (adjusted mean difference = 9.43mm; 95% CI = 0.46, 18.40;  $p = 0.039$ ). Across all time points there was also a significant difference in cyclical pain favouring the electrodiathermy group (adjusted mean difference

= 10.13mm; 95% CI = 3.48, 16.78;  $p = 0.003$ ). Crucially, neither of these effects attained the prespecified MID of 18.00mm.

There was a significant difference at 12 weeks in dyspareunia in favour of the electrodiathermy group, though of smaller magnitude than the MID (adjusted mean difference = 11.66mm; 95% CI 1.39, 21.93;  $p = 0.026$ ), but differences in other secondary outcomes at 12 weeks were non-significant (Table 3).

Profile plots for cyclical pain and dyspareunia (adjusted mean values) are shown in Figure 2, showing a somewhat greater difference towards the end of the follow-up period for cyclical pain, but a fairly consistent effect over time in relation to dyspareunia.

Averaging across timepoints, there were significant differences in favour of the electrodiathermy group in respect of three subscales of the EHP-30: pain, emotional well-being, and self-image (Table 3).

Mean (SD) intraoperative blood loss was 24 (29) ml (range 0ml–200ml) in the electrodiathermy group and 15 (17) ml (range 0–100ml) in the helium group. Following a natural-logarithm transformation of the data (owing to violations of the assumptions of normality and homogeneity of variance of the residuals), this difference was tested through a  $t$  test; the back-transformed data are expressed as a fold change. Compared to the helium group, blood loss in the electrodiathermy group was 1.43 times greater (95% CI 0.96, 2.15), but this

effect was not statistically significant ( $t = 1.757$ ;  $p = 0.081$ ). No visceral complications were noted, nor any post-operative complications.

The operative duration was slightly longer in the electrodiathermy group (mean = 37.66mins, SD = 12.56; 2 missing values) than in the helium group (mean = 36.02mins, SD = 11.89; 6 missing values). This difference of 1.64mins was not significant ( $t = 0.907$ ;  $p = 0.365$ ). Among women who had tried to become pregnant following surgery ( $n = 81$ ), 17/44 (38.6%; 11 missing values) in the electrodiathermy and 9/37 (24.3%; 14 missing values) in the helium group had succeeded in doing so. This difference was not significant (odds ratio with electrodiathermy as reference category = 0.554, 95% CI = 0.200, 1.481;  $p = 0.234$ ); given maximum likelihood estimation, the 25 missing values in this analysis were not imputed.

A secondary unadjusted analysis on the primary outcome measure yielded a significant, but smaller, effect across all time points (mean difference = 7.90mm; 95% CI = 0.60, 15.20;  $p = 0.034$ ). The effect at 12 weeks was non-significant (mean difference = 6.42mm; 95% CI = -2.93, 15.77;  $p = 0.177$ ).

## **DISCUSSION**

### **Main findings**

In this randomized controlled trial comparing the effect of treatment of mild-to-moderate endometriosis with electrodiathermy or helium thermal coagulator, a statistically significant difference in cyclical pain scores was detected at 12

weeks in favour of electrodiathermy. Across all time points there was also a statistically significant difference in cyclical pain in favour of the electrodiathermy group. For the secondary outcome measures, statistically significant differences favoured electrodiathermy for dyspareunia at 12 weeks. The effects seen on cyclical pain and dyspareunia were, however, both smaller than the proposed MID and therefore cannot be assumed to be clinically important. Small but statistically significant differences in some quality of life measures (pain, emotional wellbeing and self-image) also favoured the use of electrodiathermy.

### **Strengths and limitations**

This trial provides high-quality evidence comparing the use of a helium thermal coagulator to electrodiathermy in the treatment of mild-to-moderate endometriosis. Its design was informed by the perspectives of patients, and their views on outcomes measures and timing of follow-up were particularly helpful. The study was double-blinded, except for the surgeon, who of necessity was not blind to the intervention. Only one woman failed to receive the assigned intervention. Analysis was performed on an intention-to-treat basis and steps were put in place to minimize loss to follow-up.

Over-recruitment to meet the desired sample size was needed due to a larger-than-expected number of participants being rejected in theatre prior to randomization ( $n=106$ ). This was due either to absence of disease or to disease classified as more severe than mild-to-moderate, and suggests the

need for a more effective way to determine which patients will benefit from laparoscopic surgery.

### **Interpretation**

Meta-analysis of laparoscopic treatment of endometriosis has shown a superior reduction in symptoms compared to diagnostic laparoscopy alone.<sup>7</sup> Defining which laparoscopic technique yields the best results has been the focus of much debate and research. In our trial, participants in both treatment arms could receive ablation and/or excision, according to clinical judgment. Other trials that have specifically compared ablation to excision of endometriosis have demonstrated comparable reduction in severity of symptoms.<sup>12,21,22</sup> Meta-analysis, however, has shown greater improvement in symptoms of endometriosis at 12 months with excision than with ablation.<sup>23</sup>

It has been suggested that the benefit of excision is the removal of deep disease, conferring better symptomatic relief than ablation, which may just treat superficial disease, leaving deeper disease behind. We theorize that this is the likely mechanism by which electrodiathermy showed statistically superior results in this trial – albeit not of clinical significance – as excision was much more commonly performed with this technique than with the helium thermal coagulator. As traditional electrodiathermy allows for the excision of deeper endometriotic tissues it may therefore provide a greater degree of reduction in symptoms such as pain and dyspareunia that are considered to be associated with deeper disease.

In this study, helium coagulation was not shown to be clinically superior to electrodiathermy in the laparoscopic treatment of mild-to-moderate endometriosis. Surgeons may therefore choose to base their choice of intervention on other considerations. Faced with disease overlying delicate structures such as bladder, bowel and diaphragm, they may favour the use of helium coagulation, owing to its low thermal spread. Conversely, a desire to achieve deeper excision may prompt them to use electrodiathermy.

The interventions performed in this study were undertaken by surgeons working in an accredited endometriosis centre and the results obtained may not reflect those achieved by a general gynaecologist. For example, the excision performed through electrodiathermy may have been fuller and deeper than that undertaken by a generalist.

## **CONCLUSION**

In conclusion, although laparoscopic treatment of mild-to-moderate endometriosis with electrodiathermy showed statistically significant superior improvement in symptoms of cyclical pain, dyspareunia and some quality of life measures when compared with treatment with a helium thermal coagulator, the magnitude of these effects was generally too small to infer that they are clinically important. Further research, including health economics evaluation, is needed before clear recommendations can be made for clinical practice.



### **Disclosure of interests**

The authors declare no conflicts of interest.

### **Contribution to authorship**

GM, JS, ZEG, SOB and KW contributed to the conception and design of the study. GM and ZEG performed the clinical interventions. SJ managed outcome assessment. JS analysed the data. JS, GM, TC and JR drafted the paper. All authors reviewed the manuscript and approved the final version.

### **Details of ethical approval**

The study was approved on 3<sup>rd</sup> October 2013 by the NRES East Midlands – Leicester Ethics Committee (13/EM/0354) and registered in December 2013 (ISRCTN 50928834).

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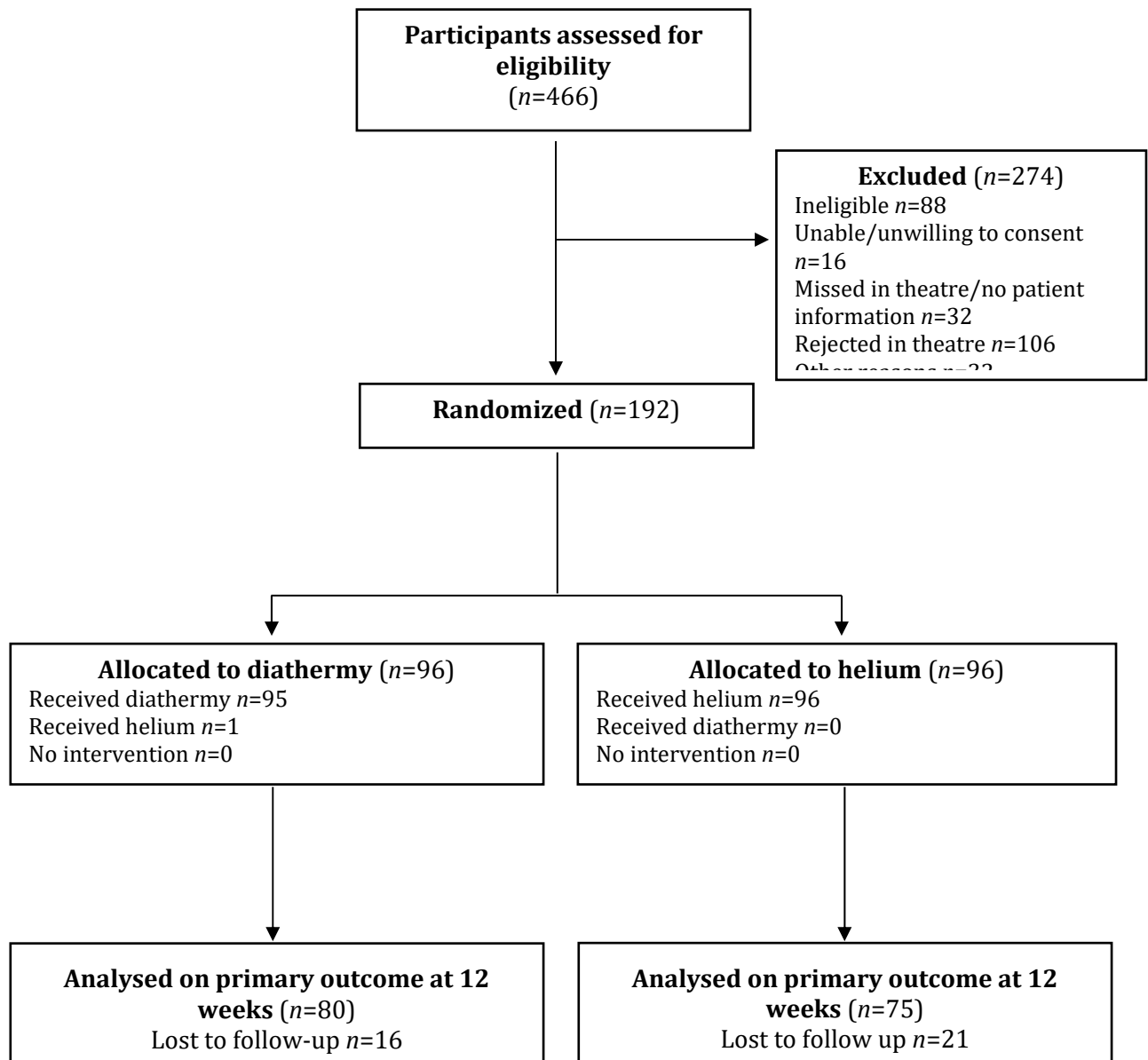
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**Figure 1.** CONSORT diagram.

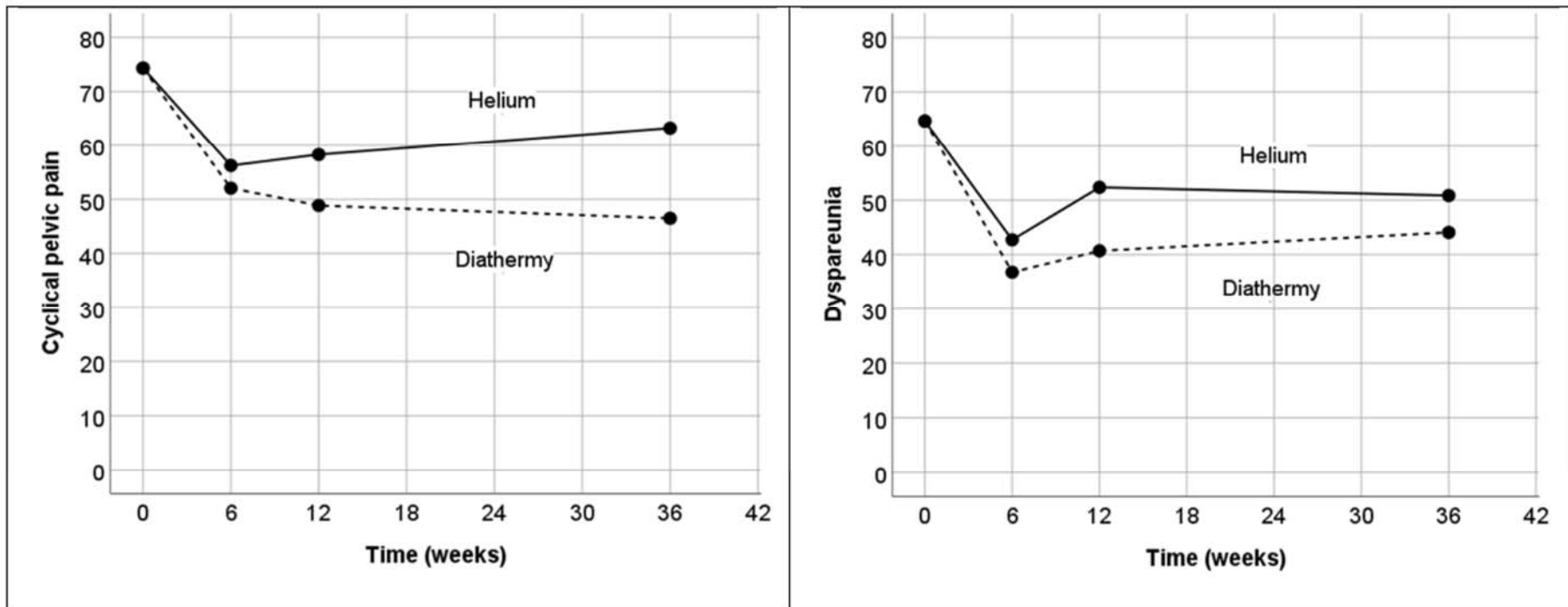


**Table 1.** Baseline characteristics ( $n = 192$ ). Values are mean (standard deviation) unless otherwise indicated.

		<b>Diathermy (<math>n = 96</math>)</b>	<b>Helium (<math>n = 96</math>)</b>
Age (years)		28.99 (6.99)	29.03 (7.11)
VAS score for cyclical pain (mm) <sup>a</sup>		76.52 (19.65)	72.14 (20.68)
VAS score for dyspareunia (mm) <sup>b</sup>		62.79 (30.49)	66.49 (27.53)
EHP-30 pain		59.00 (20.04)	56.46 (19.74)
EHP30 control and powerlessness		71.35 (22.95)	69.03 (22.93)
EHP-30 emotional well-being		55.86 (21.33)	56.79 (22.30)
EHP-30 social support		61.65 (25.11)	57.68 (27.48)
EHP-30 self-image		59.72 (27.30)	57.60 (30.85)
Surgeon; $n$ (%)	A	64 (67)	72 (75)
	B	32 (33)	24 (25)
RASRM grade; $n$ (%)	1	39 (41.5)	37 (41.6)
	2	49 (52.1)	50 (56.2)
	3	6 (6.4)	2 (2.2)
Previous laparotomy or laparoscopy; $n$ (%) <sup>d</sup>	Yes	46 (48.9)	42 (46.7)
	No	48 (51.1)	48 (53.3)

<sup>a</sup> 4 missing values,  $n_1=93$ ,  $n_2=95$ ; <sup>b</sup> 6 missing values,  $n_1=92$ ,  $n_2=94$ ; <sup>c</sup> 9 missing values  $n_1=94$ ,  $n_2=89$ ; <sup>d</sup> 8 missing values  $n_1=94$ ,  $n_2=90$ . EHP-30 = Endometriosis Health Profile (each dimension scored 0–100; lower scores indicate better quality of life). RASRM grade = Revised American Society for Reproductive Medicine endometriosis classification. VAS = visual analogue scale.

**Figure 2.** Profile plots for cyclical pain and dyspareunia (covariate-adjusted mean values)





**Table 2.** Values of outcome variables at follow-up. Values are mean (standard deviation).

	6 weeks			12 weeks			36 weeks		
	Diathermy	Helium	<i>n1, n2</i>	Diathermy	Helium	<i>n1, n2</i>	Diathermy	Helium	<i>n1, n2</i>
VAS score for cyclical pain (mm)	48.01 (28.15)	50.64 (30.20)	82, 75	45.56 (28.80)	52.68 (31.60)	80, 75	41.88 (33.03)	58.47 (29.35)	58, 59
VAS score for dyspareunia (mm)	33.54 (32.25)	40.69 (36.44)	79, 71	38.67 (32.10)	52.23 (37.42)	72, 70	38.20 (36.66)	49.43 (38.53)	55, 56
EHP-30 pain	34.50 (23.03)	39.81 (25.69)	88, 83	32.44 (26.61)	37.22 (27.17)	81, 77	35.19 (28.05)	41.87 (26.17)	60, 59
EHP-30 control & powerlessness	40.62 (27.58)	47.39 (30.88)	88, 83	41.05 (32.64)	45.18 (34.24)	81, 77	44.79 (32.67)	49.58 (32.48)	60, 59
EHP-30 emotional well-being	35.75 (23.79)	44.02 (25.55)	88, 83	35.19 (26.96)	41.72 (28.97)	81, 77	39.10 (28.49)	45.27 (27.86)	60, 59
EHP-30 social support	42.26 (29.07)	46.16 (30.69)	88, 83	45.83 (34.29)	46.51 (34.20)	81, 77	44.27 (35.06)	49.89 (30.65)	60, 59
EHP-30 self-image	40.53 (31.01)	46.49 (31.43)	88, 83	44.86 (35.42)	45.13 (35.16)	81, 77	43.47 (32.98)	47.03 (35.14)	60, 59

EHP-30 = Endometriosis Health Profile (each dimension scored 0–100; lower scores indicate better quality of life). VAS = visual analogue scale.

**Table 3.** Estimates of mean differences in secondary outcome variables at 12-week follow-up and averaged across all follow-up timepoints (differences are helium group minus electrodiathermy group). Values are derived from linear mixed models (including all randomized participants) adjusted for baseline value, age, surgeon, Revised American Society of Reproductive Medicine classification, and previous abdominal surgery.

	<b>12-week follow-up: difference (95% CI); <i>p</i> value</b>	<b>All follow-up timepoints: difference (95% CI); <i>p</i> value</b>
VAS score for dyspareunia (mm)	11.66 (1.39, 21.93); 0.026	8.13 (−0.08, 16.34); 0.052
EHP-30 pain	6.38 (−0.88, 13.64); 0.085	6.32 (0.49, 12.15); 0.034
EHP-30 control and powerlessness	4.94 (−3.68, 13.56); 0.259	5.47 (−1.65, 12.58); 0.131
EHP-30 emotional well-being	6.47 (−0.13, 13.08); 0.055	5.54 (0.00, 11.08); 0.050
EHP-30 social support	5.05 (−3.59, 13.68); 0.250	5.60 (−1.10, 12.308); 0.101
EHP-30 self-image	5.79 (−2.33, 13.91); 0.161	7.16 (0.10, 14.22); 0.047

CI = confidence interval; EHP-30 = Endometriosis Health Profile (each dimension scored 0–100; positive differences indicate better quality of life in the electrodiathermy group). VAS = visual analogue scale; positive differences indicate less dyspareunia in the electrodiathermy group).