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Medical management of deeply infiltrating endometriosis - 7 year experience in a tertiary endometriosis centre in London

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Abstract

Background: Deeply infiltrating endometriosis has an estimated prevalence of 1% in women of reproductive age. Ninety percent have rectovaginal lesions but disease may also include the bowel, bladder and ureters. Current practice often favours minimally invasive surgical excision; however, there is increasing evidence that medical management can be as effective as long as obstructive uropathy and bowel stenosis are excluded. Our objective was to establish the proportion of women with deeply infiltrating endometriosis successfully managed with hormonal therapies within our tertiary endometriosis centre in West London. Secondary analysis was performed on anonymised data from the Trust's endometriosis database.

Results: One hundred fifty-two women with deeply infiltrating endometriosis were discussed at our endometriosis multidisciplinary meeting between January 2010 and December 2016. Seventy-five percent of women underwent a trial of medical management. Of these, 44.7% did not require any surgical intervention during the study period, and 7.9% were symptomatically content but required interventions to optimise their fertility prospects. Another 7.0% were successfully medically managed for at least 12 months, but ultimately required surgery as their symptoms deteriorated. 26.5% took combined oral contraceptives, 14.7% oral progestogens, 1.5% progestogen implant, 13.2% levonorgestrel intrauterine device, 22.1% gonadotrophin-releasing hormone analogues, and 22.1% had analogues for 3–6 months then stepped down to another hormonal contraceptive. All women who underwent serial imaging demonstrated improvement or stable disease on MRI or ultrasound.

Conclusions: Medical treatments are generally safe, well tolerated and inexpensive. More than half (52.6%) of women were successfully managed with medical therapy to control their symptoms. This study supports the growing evidence supporting hormonal therapies in the management of deeply infiltrating endometriosis. The findings may be used to counsel women on the likely success rate of medical management.

Keywords: Endometriosis, Deeply infiltrating endometriosis, Pelvic pain, Hormonal therapy, Medical management, Contraceptive, Progestogen, Combined oral contraceptive, Levonorgestrel-releasing intrauterine system, Gonadotrophin-releasing hormone

Background

Endometriosis is a chronic oestrogen-driven condition characterised by the presence of ectopic endometrial glands and stroma outside the endometrial cavity. Deeply infiltrating endometriosis (DIE) is defined as endometriotic tissue found more than 5 mm below the peritoneal surface. It has an estimated prevalence of 1% in women of reproductive age—90% have rectovaginal lesions but disease may also include the bowel, bladder, and ureters [1].

Evidence supporting the use of hormonal therapies in the management of women with symptomatic DIE has been accumulating since the early 2000s [2–8]. In 2013, a small Italian study [9] demonstrated a reduction in mean rectovaginal nodule volume in women using various forms of medical management for over 12 months. Despite this, current practice favours laparoscopic surgical excision, largely due to a belief amongst gynaecological surgeons that medical treatment is ineffective in

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complex disease. A review article published in 2017 [10] went as far to say: 'It is widely agreed that severe endometriosis, especially in symptomatic DIE with colorectal extension, requires surgical treatment'. It is worth remembering that a significant number of women with rectovaginal disease are in fact asymptomatic, and never need any treatment. To be able to manage symptomatic disease with relatively simple, reversible medical treatments is an attractive solution. This approach has the advantage of avoiding patient morbidity associated with complex surgery, including complications such as haemorrhage, infection and bladder, bowel or ureteric injury. It further avoids the consequences of bowel surgery including the need for temporary stoma, fistulae and anastomotic leaks. Bowel resection of rectovaginal endometriosis is likely to be associated with a higher incidence of complications than resections performed for other diagnoses [11]. Although there has been a substantial shift towards more conservative surgery in recent years (such as rectal shave in preference to excisional resection [11, 12], and nerve-sparing surgery [13–15]), there has not been a concurrent trend towards conservative or medical therapy. In the longer term, the inevitable neurological damage sustained during radical dissection, causing constipation, voiding difficulties and sexual dysfunction may be circumvented by using medical therapies first-line.

Our objective was to determine the rate of successful medical management in women with DIE within our endometriosis service. The Trust is accredited by the British Society for Gynaecological Endoscopy (BSGE) as an Endometriosis Surgical Centre. The monthly endometriosis multidisciplinary team meeting (MDT) is attended by a dedicated team of gynaecological surgeons, radiologists, colorectal surgeon, urologist, fertility specialist and nurse specialist.

Methods

We performed a retrospective observational study of women with DIE discussed at the Imperial College Healthcare NHS Trust Endometriosis MDT between January 2010 and December 2016. The Trust is based in West London and is made up of two tertiary units—St Mary's Hospital, and Queen Charlotte's and Chelsea Hospital. The project was registered and approved with the Trust's Audit Department. Secondary analysis was performed on fully anonymised data; therefore, as per national and international guidelines, ethical approval was not sought.

Women had been identified from the Endometriosis MDT database, and manual case note review was performed to confirm the presence of DIE. Specifically, we reviewed the patient's imaging reports within the previous 12 months to identify evidence of endometriotic nodules or plaques involving the rectum, bowel, bladder and/or ureters. Women who had undergone recent diagnostic surgery (within the last 12 months) demonstrating DIE were also included. Women without good evidence of DIE, including those with ovarian endometriomas or 'kissing ovaries' alone, were excluded. The paper and electronic medical records of women with DIE identified on pelvic imaging and/or at laparoscopy were examined. Data collected included (1) previous medical and surgical management, (2) imaging modality and results, (3) management plan made at the Endometriosis MDT meeting, (4) subsequent medical and surgical management, (5) number of appointments with the surgical team(s), (6) endometriosis clinic status including referral to other clinical teams and (7) complications. Documented communication and written correspondence between the patient, endometriosis team members and general practitioner were also extensively reviewed to make an assessment of the patient's symptoms at presentation and following treatment. Follow-up of the women's clinical progress continued up until January 2018.

Results

Two hundred three women were discussed at the Imperial College Healthcare NHS Trust MDT between January 2010 and December 2016. Fifty-one women were excluded. Forty-one did not meet the criteria to diagnose DIE, and 10 case notes could not be obtained via medical records. This left a total of 152 women.

The mean and median age of women at the time of MDT discussion was 37 (range 24–57 years). Sixteen women were discussed in the endometriosis MDT meeting more than once. Women included in the analysis were diverse in regards to their symptoms, severity of disease and previous medical and surgical managements. 70.4% (107/152) of women had tried some form of hormonal therapy prior to referral to the endometriosis service, with 21.7% (33/152) trying more than one preparation. The most frequently used preparations were the combined contraceptive pill and gonadotrophin-releasing hormone (GnRH) analogues. However, 29.6% (45/152) women had not tried any form of medical management in the past, even for the purposes of contraception. 27.6% (42/152) of women had not had any form of surgical intervention for endometriosis or pelvic pain in the past. 50.7% of women (77/152) had one previous surgical procedure and 5.3% (8/152) of women had undergone at least two surgical procedures. Table 1 is a summary of the relevant surgical procedures women had undertaken prior to MDT discussion.

Seventy-five percent (114/152) of women with DIE underwent a trial of medical management. Medical management was theoretically inappropriate in the remaining cases—15 women wanted to conceive, 14 declined and 9

Table 1 A summary of the surgical procedures performed prior to MDT discussion

Previous surgery	Total	Laparoscopic	Open
Complex endometriosis surgery	17	7	9
Rectal shave	6		
Bowel resection	7		
Resection of ureteric nodule	3		
Resection of bladder nodule	1		
Ovarian cystectomy/drainage of endometrioma ± ablation of cyst wall	46	33	13
Oophorectomy	1	1	
Diathermy or laser to superficial disease	35	35	
Diagnostic laparoscopy	31		
Myomectomy	8	3	5
Hysterectomy ± salpingoophorectomy	3	2	1
Video-assisted thoracoscopic surgery (VATS) Pleurodesis for haemothorax	1		
Excision of endometriotic umbilical nodule	1		

were asymptomatic or postmenopausal. Seven women cited intolerable side effects as the reason for declining a further trial of medical management. There were no cases of obstructive uropathy, bowel stenosis or other medical contraindications to hormonal therapies.

Table 2 demonstrates the outcomes of women managed within the endometriosis service over the 7-year study period. Out of the 114 women who accepted medical management, 44.7% did not require any surgical or other intervention during the study period, and 7.9% were symptomatically content on medical management but sought to conceive within 12 months of initiating hormonal treatment. Of these, three women required surgery to optimise their fertility prospects in preparation for oocyte retrieval and in vitro fertilisation. Drainage, ablation and/or excision of large (> 5 cm) endometriomas, freeing of the ovaries and salpingectomy/tubal clipping were performed as necessary. Six women proceeded directly to an in vitro fertilisation cycle. Another 7.0% were successfully medically managed for at least 12 months, but ultimately chose surgery as their symptoms deteriorated. Therefore, 52.6% of women were successfully managed with medical therapy to control their symptoms.

37.7% of women were initiated on a treatment they had tried in the past. Of those successfully medically managed, 26.5% took combined oral contraceptives, 14.7% oral progestogens, 1.5% progestogen implant, 13.2% levonorgestrel intrauterine device and 22.1% GnRH analogues, and 22.1% had GnRH analogues for

Table 2 Outcomes of women managed within the endometriosis service over the 7-year study period

	Total (%)	Combined oral contraceptives	Progestogens–oral	Progestogens–depo/implant	Progestogens–levonorgestrel releasing IUS	GnRH Analogues ± HRT	GnRH Analogues 3–6 months, followed by a contraceptive
Good control of symptoms—no further surgery required	51 (33.6)	14	8	1	7	8	13
Good control of symptoms—wanted to conceive within 12 months	9 (5.9)	2	2	0	1	4	0
Good control of symptoms for over 12 months—surgery ultimately required	8 (5.3)	2	0	0	1	3	2
Poor control of symptoms—surgery required	46 (30.3)	3	3	0	2	38	0
Poor control of symptoms—wanted to conceive	15 (9.9)	–	–	–	–	–	–
Declined medical management	14 (9.2)	–	–	–	–	–	–
Asymptomatic/postmenopausal	9 (5.9)	–	–	–	–	–	–

3–6 months then stepped down to another hormonal contraceptive. In the 51 women who aimed to continue long-term medical management, the mean duration of hormonal therapy was 22 months. The maximum recorded duration of treatment was 110 months, using the levonorgestrel intrauterine device.

Of the 17 women who already had complex surgery for deeply infiltrating endometriosis in the past, 11 had successful medical management. Two of these women ceased treatment within 12 months to try to conceive. Three women declined hormonal therapies, and three women had poor symptom control on medical treatments and required surgery. Four women underwent pelvic clearance and two women had repeat conservative surgery performed laparoscopically. Of the 14 women who accepted a trial of medical management, 7 women had GnRH analogues, 6 took combined oral contraceptive pills and one women opted for the levonorgestrel intrauterine device. All three women with poor symptom control on medical management were using GnRH analogues.

Out of 114 women, 5 complained of bothersome side effects as a result of medical management. Three women opted for surgical management following a trial of GnRH analogues, despite the addition of add-back hormone replacement therapy (HRT). One woman was switched to an oral progestogen and successfully continued with long-term medical management. The fifth woman took GnRH analogues with add-back HRT for 12 months but did not require further treatment as her symptoms had improved.

Pelvic magnetic resonance imaging (MRI) is the primary mode of imaging used to screen for DIE within the Trust. 98.6% women underwent a pelvic MRI within 12 months of the MDT. 58.6% women underwent a pelvic ultrasound within 12 months. Sixteen women who underwent a trial of medical management had serial imaging performed during the study period. Five women had demonstrated improvement in their imaging findings, with a reduction in the size of endometriotic nodules and/or endometriomas. Eleven women had stable disease and none demonstrated progression of disease during the study period.

The average number of visits to the endometriosis clinic before and after the Endometriosis MDT meeting was 2.3. Table 3 demonstrates that there was no significant difference between women treated medically versus surgically, in terms of the number requiring continued follow-up, referral to other specialties of relevance, or those discharged from the endometriosis clinic (p value > 0.05 using N–1 Chi squared test).

Discussion

Our analysis suggests that in women with DIE who find medical treatment acceptable, more than half (52.6%) can be treated successfully with combined contraceptives, progestogens and/or gonadotrophin-releasing hormone analogues. Women who have previously undergone complex excisional surgery, with recurrent or intractable symptoms, can also be successfully medically managed. Our experience illustrates that evidence from clinical trials can be applied to clinical practice. It supplements the growing evidence in support of hormonal therapies as a valid, long-term option in the management of DIE.

Medical treatments are generally safe, effective and inexpensive. Side effects are uncommon, reversible and well tolerated in the majority of women. If side effects are troublesome, a change in preparation can often be considered. GnRH analogues can have more severe hypoestrogenic side effects, including implications for bone density in the long term. In our patient group, GnRH analogues were most often used in the short term for relatively rapid control of pain and induction of amenorrhoea, before introducing another hormonal treatment such as the levonorgestrel IUS. A smaller number of older women remain on long-term downregulation with two yearly monitoring of their bone density. To address the impact on bone density and menopausal symptoms, we typically offer hormonal add-back therapy to coincide with commencement of GnRH analogues, as per current European guidance [16].

Improvements in diagnostic imaging mean that the diagnosis of DIE can be made in the absence of laparoscopy. Furthermore, screening for ureteric stenosis, hydronephrosis and bowel stenosis can be performed confidently by specialist ultrasonographers or by

Table 3 Endometriosis clinic status—comparison of women treated medically and surgically

Clinic status	Medical management	Surgical management	p value*
Discharged from the endometriosis clinic	35	42	0.58
Referred onwards to fertility team	9	16	0.20
Referred onwards to chronic pain team	1	1	–
Referred onwards to colorectal team	1	0	–
Under follow-up	20	13	0.09
Lost to follow-up	2	3	–

*Determined by N–1 Chi squared test. The results are not significant at $p < 0.05$

magnetic resonance imaging [17]. The need for laparoscopy in the assessment of DIE is therefore reduced, and women can be counselled regarding the pros and cons of conservative, medical and surgical managements.

The ideal drug to treat DIE should downregulate proliferation, preclude invasion and encourage apoptosis by acting on the hormonal and immunologic environment [18]. Progestogens and combined oral contraceptives have already been demonstrated to decrease the densities of sympathetic, parasympathetic and sensory nerve fibres in DIE [19].

Several systematic reviews [20–22] have directly compared medical treatments with surgery in the management of endometriosis, but the literature is much scantier when focussing on DIE. A prospective clinical trial [9] included 79 women with rectovaginal nodules infiltrating at least the muscularis propria of the rectum who received one of the following: norethisterone acetate, triptorelin and tibolone, norethisterone acetate and letrozole, desogestrel and sequential oral contraceptive pill. When compared with baseline values, the volume of the nodules decreased at 6 months ($p < 0.001$) and 12 months of treatment ($p < 0.001$). After 12 months of treatment, the mean volume of rectovaginal nodules decreased in all study groups. The effectiveness of the levonorgestrel-releasing intrauterine system has also been studied for the management of rectovaginal endometriosis. Fedele et al. [3] demonstrated a significant improvement in dysmenorrhoea, pelvic pain, deep dyspareunia and size of endometriotic nodules following 12-month treatment with the levonorgestrel-releasing intrauterine system. A small proportion of nodules will increase in volume, and women should be informed of this [6, 9, 23].

A randomised control trial [2] also demonstrated a lack of progression of existing endometriomas, and inhibition of development of new endometriomas with oral progestogens and the combined oral contraceptive pill. Studies looking at the combined contraceptive pill, gonadotrophin-releasing hormonal agonists and dienogest in the management of bladder endometriosis have also been promising, with complete or near-complete regression of bladder nodules [4, 24].

Patient satisfaction rates and quality of life are similar in women with endometriotic lesions treated medically versus treatment by laparoscopic excision [25, 26]. All hormonal treatments have been proven to be effective in the treatment of dysmenorrhoea, pelvic pain, dyspareunia and gastrointestinal symptoms associated with DIE [3, 23, 27–30]. Unfortunately, early symptom recurrence is common following treatment cessation, and therefore short-term treatment is unlikely to be beneficial [7, 30]. Recurrence following laparoscopic excision of rectovaginal endometriosis is also well documented, and estimated to be between 5 and 25% [31]. Repeated surgery for DIE becomes increasingly challenging due to loss of normal tissue planes. The ideal scenario would be for women to be managed medically during their reproductive years, and opt for pelvic clearance once their family is complete, if medical management is no longer feasible. It is our opinion that any strategy that can successfully reduce the need for surgery should be embraced.

Strengths and limitations

Women in this study were identified from the Trust's Endometriosis MDT Database. We are aware that some women with DIE were not discussed with the multidisciplinary team following review in the endometriosis clinic. These women were managed with hormonal therapies and have remained stable on treatment, therefore would not usually necessitate MDT discussion. It is our normal practice for a woman with DIE being considered for surgical management to be discussed in the MDT meeting. Consequently, the proportion of women with DIE successfully medically managed within the Trust is likely to be higher than described.

The significance of bias caused by loss to follow-up is likely to be minimal, and analysis was performed on an intention to treat basis. Only seven women did not complete follow-up with the endometriosis service; two of whom had started medical management. Both women were reviewed 6 months after initiating hormonal treatment and were symptomatically content. Out of the remaining women lost to follow-up, three were recommended to undergo surgery and had a high chance of requiring bowel resection. Two women were asymptomatic at presentation and had been counselled towards conservative management. Without a national hospital records system, it is difficult to assess the probability, or impact of women seeking treatment in other units.

An accepted limitation of our study is the retrospective, observational design and reliance on accurate documentation by clinicians involved in the patient's care. Patient heterogeneity in terms of demographics, reported symptoms, disease severity and previous treatments is high. It is difficult to account for the impact of potential confounders, given the variety and diversity of variables. For example, there was inconsistent documentation of complementary treatments, such as exclusion diets, which may have affected symptomatology. A prospective study using a patient questionnaire and validated tools to assess symptoms and quality of life could address this issue.

Conclusions

The management of women with endometriosis should continue to be based on a variety of factors, such as the women's symptoms, severity of disease, impact on

quality of life, fertility status and taking in to account previous treatments and their outcomes. Women with DIE should be managed as part of a multidisciplinary team in an endometriosis centre [32].

The results of this study add further support to the medical management of women with DIE. Women should be informed that medical management can be effective in managing their symptoms and disease, and has the advantage of avoiding the risks associated with complex surgery. Given that nerve-sparing surgeries are still performed by the minority of endometriosis surgeons, the incidence of neurological trauma causing constipation, voiding difficulties and sexual dysfunction may be reduced. Furthermore, hormonal therapies are generally safe, well tolerated and inexpensive.

Research recommendations

In the absence of the ability to perform a randomised controlled trial with long-term follow-up, more high quality prospective cohort studies should be designed. Ideally, these would investigate the clinical and radiological progress of women with DIE treated conservatively and with various hormonal therapies. Patient satisfaction and quality of life could be assessed by a patient questionnaire using validated tools. The British Society for Gynaecological Endoscopy currently holds a database of women with DIE treated surgically in their centres—we see no reason why a similar database for women managed medically could not be constructed, maintained and analysed in a similar fashion.

Abbreviations

DIE: Deeply infiltrating endometriosis; MDT: Multidisciplinary team; GnRH: Gonadotrophin-releasing hormone; HRT: Hormone replacement therapy

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Authors' contributions

TM, AA and MW were responsible for the conception and design of this study. MW and AA were responsible for data acquisition. MW was responsible for data analysis. MW, TM, GR and MC were responsible for data interpretation. MW drafted the manuscript. MW, TM, AA, GR and MC all critically revised the manuscript and gave final approval for publication.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available as they contain information that could compromise patient confidentiality. They are available from the corresponding author on reasonable request.

Ethics approval

According to National Research Ethics Service (NRES) standards, ethics approval was not necessary due to the retrospective, observational nature of the study. Secondary analysis was performed on fully anonymised data collected for the purposes of departmental audit and service evaluation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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