

Short Communication

## Simultaneous use of a levonorgestrel intrauterine system and an etonogestrel subdermal implant for debilitating adolescent endometriosis

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### Abstract

Adolescent familial endometriosis may cause severe and persistent symptoms that are disruptive to lifestyle. Treatment may be difficult in many cases. We describe the novel and successful first use of a simultaneous combination of a levonorgestrel intrauterine system and an etonogestrel subdermal implant in a teenager with severe pain symptoms as a result of laparoscopically confirmed endometriosis, which was refractory to other treatments.

**Key words:** adolescence, endometriosis, etonogestrel-subdermal implant, levonorgestrel intrauterine system.

### Introduction

Endometriosis affects 6–20% of women of reproductive age. It has been reported in adolescents as young as 8 years of age, and even prior to menarche. Only recently has it been widely recognised that endometriosis often begins in adolescence, leading to major delay (up to 10 years) in diagnosis.<sup>1</sup> In a survey of 750 women conducted by the Endometriosis Association of Victoria in 1990, the average time between the onset of symptoms in teenagers and the diagnosis of endometriosis was 8.8 years, whereas the average interval for women with onset of symptoms in their thirties was only 1.5 years.<sup>2</sup> Many of these young women have debilitating and progressive symptoms of dysmenorrhoea and chronic pelvic pain that are often not well managed by health professionals.

The prevalence of endometriosis in those adolescents who have chronic pelvic pain and dysmenorrhoea, which do not respond to conventional treatment, is around 70%.<sup>3</sup> The optimal management of endometriosis continues to be a challenge, and it is more challenging in adolescence because of difficulties in history-taking, examination, confirmation of diagnosis, tolerance of pain symptoms, drug side-effects and compliance with medications. The goal of therapy is to minimise pelvic pain and dysmenorrhoea, greatly improve quality of life and protect fertility, either by 'curative' surgery or by long-term medical therapy. Adolescents with endometriosis frequently require long-term medical management until they have met and completed their child-bearing goals. Some of these young women are exceedingly difficult to manage. We

present one such case that has finally been managed successfully by combined use of the levonorgestrel-releasing intrauterine system (LNG IUS; Mirena, Schering Health, Berlin, Germany) and etonogestrel-releasing subdermal implant (Implanon, Organon, OSS, The Netherlands) after failure of other medical therapies.

### Case report

The patient first presented at age of 13 (April 2002), with an episode of right iliac fossa pain that built up steadily and required general surgical consultation. No diagnosis was made and no therapy was given. This was followed a few weeks later by an episode of sudden and more acute lower abdominal pain requiring hospitalisation. Abdominal ultrasound scan revealed several ovarian follicles but no abdominal or pelvic pathology. The pain settled spontaneously but then recurred. Laparoscopy by a general surgeon revealed 'old blood' in the pelvis and a fimbrial cyst that was removed. A mildly inflamed appendix (confirmed on pathology) was also removed. No mention of endometriosis was made. Menarche

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**Table 1** List of medications used by this patient over a three-year period for treatment of symptoms of endometriosis or for the relief of side-effects of the medications

No	Name of drug	Age (years)	Duration	Indication	Effect
1	Combined oral contraceptive	13	2 months	Acne, dysmenorrhoea, pelvic pain	Acne improved, pain the same
2	NSAIDs (Ponstan, Naprogesic)	13	Most of the time	Chronic pelvic pain, dysmenorrhoea	Minor benefit
3	Microgynon 30, Yasmin	13	4 months	Endometriosis pain	BTB, headache, pain the same
4	Zoladex	14	6 months	Endometriosis pain	Hot flushes +++, good pain control
5	Kliovance	14	1 month	Hot flushes during Zoladex	Hot flushes improved
6	Medroxyprogesterone Acetate 10 mg b.i.d.	14–15	3 years	Endometriosis pain	Amenorrhoea, pain partially reduced but abdominal bloating +++
7	Norethisterone 10 mg t.i.d.	15	2 months	Endometriosis pain	Pain partially reduced but BTB +++, acne ++
8	Tamoxifen 10 mg	15	2 months	Endometriosis pain, BTB, acne	Pain partially reduced but breast tenderness +++
9	Mirena Implanon	15	One year continuing	Endometriosis pain	Greatly improved – virtually pain-free
10	Efexor 37.5 mg	15	2 weeks	Reactive depression	Cured

++ moderate, +++ severe. BTB, breakthrough bleeding.

had occurred at age of 12 and was followed by early establishment of a fairly regular, monthly cycle with heavy periods, but no initial pain. Dysmenorrhoea developed within one year after menarche, shortly before her presentation at age 13.

Recurrence and exacerbation of severe pelvic pain lead to a further diagnostic laparoscopy (by an experienced gynaecologist) in October 2002, where extensive classical peritoneal endometriosis was found and partially treated by bipolar diathermy. A series of medical therapies was initiated (Table 1), none of which was ideal, either causing troublesome side-effects or not improving symptoms. Goserelin implant (Zoladex, AstraZeneca, North Ryde, NSW, Australia) was the only medication to substantially abate pain, but caused very troublesome hot flushes (treated with Kliovance). Although the use of oral progestogens partially reduced the pelvic pain, both abdominal bloating and breakthrough bleeding (with troublesome cramps) increased markedly with these agents.

Eventually, it was decided that constant systemic delivery of progestogen could be valuable and that the increasing evidence supporting use of the LNG IUS and the etonogestrel-releasing subdermal implant system in endometriosis could be usefully combined to ensure both systemic and local delivery in this difficult case. These were inserted under a brief general anaesthetic in October 2004. Pain and breakthrough bleeding have steadily settled and from six months later (aged 16), she has remained amenorrhoeic and is free of pain. She has lost 10 kg in weight, feels very well and has become sufficiently self-confident to have a boyfriend.

The patient's mother also has a long-standing history of dysmenorrhoea and erratic pelvic pain and has a laparoscopically confirmed diagnosis of endometriosis.

## Discussion

The combined use of the LNG IUS and the etonogestrel-releasing subdermal implant is a novel option in the treatment of difficult endometriosis not responding to conventional medical treatments. This case report provides some evidence that this combined therapy may effectively suppress endometriosis symptoms, at least on a medium-term basis in patients with pain that may be resistant to other therapies.

Increasing evidence points to substantial functional and morphological abnormalities in the eutopic endometrium in patients with endometriosis, including the presence of sensory C nerve fibres<sup>4</sup> and increased angiogenesis.<sup>5</sup> These facts encouraged us to locally target the endometrium with the LNG-IUS and suppress more distant ectopic implants with a constant dose of systemic progestogen through the etonogestrel implant.

Oral progestogens are cheap and can be effective, yet their efficacy can be significantly influenced by poor compliance and systemic side-effects such as irregular breakthrough bleeding, associated cramping pain, fluid retention, abdominal bloating, weight gain, increased appetite, nausea, headaches, breast tenderness and depression in a minority of users.

There is some evidence in the literature that the etonogestrel implant can be used as an option in the treatment of pain symptoms associated with endometriosis.<sup>6–8</sup> The etonogestrel implant effectively inhibits ovulation by preventing luteinizing hormones surge and also has a direct progestogenic effect by inhibiting endometrial proliferation. The LNG-IUS can be as effective as a GnRH-analog in the treatment of chronic pelvic pain associated with endometriosis.<sup>9</sup> It effectively prevents endometrial and endometriotic proliferation and greatly decreases the volume

of menstrual bleeding and tissue shedding. The LNG-IUS was associated with symptomatic relief of pain in 70% of endometriosis sufferers after 12 months therapy,<sup>7</sup> and it also appears to be a safe and effective option in nulliparous women.<sup>10</sup> There is also preliminary evidence to indicate that the LNG-IUS may be effective in preventing the recurrence of endometriosis after laparoscopic treatment.<sup>11</sup>

Among the advantages of this combined treatment is the fact that a steady low-dose delivery of progestogen is maintained, targeting both eutopic and ectopic endometria. Although it may be initially expensive, the cumulative long-term costs are likely to be less than surgical therapy and comparable with other forms of medical therapy.<sup>12</sup>

We are unaware of a combination of these progestogen delivery systems having been used previously to treat endometriosis. We have since used this combination on other young endometriosis patients with troublesome and resistant pain and believe that this approach is sufficiently promising to be formally investigated for medium- to long-term endometriosis therapy in randomised, comparative clinical trials.

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