Drugs 2001; 61 (12): 1735-1750
0012-6667/01/0012-1735/$27.50/0

Endometriosis

Aetiology, Pathogenesis and Treatment

Tim J. Child and *Seang Lin Tan*

Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

Contents

Abstract

Endometriosis, which may be defined as the presence and proliferation of endometrial tissue outside the uterine cavity, causes pain and infertility for millions of women worldwide. Studies suggest a prevalence of 0.5 to 5% in fertile and 25 to 40% in infertile women.

The most widely accepted aetiological theory is that retrograde flow of menstrual fluid through the Fallopian tubes deposits viable endometrial tissue, which implants on the peritoneal surface. Increasingly, the aetiology of endometriosis is being studied at the immunological and genetic levels.

The aim of treatment of endometriosis is to remove or diminish disease deposits. This may be attempted through medical or surgical means. It has long been recognised that endometriotic glands are hormonally sensitive. Medical therapies work by inducing a hypoestrogenic, anovulatory state to induce atrophy within the glandular tissue. Conception is generally not possible during medical therapy and has not been demonstrated to increase afterwards. Medical treatment of endometriosis should be discouraged when infertility is the primary problem. In this situation surgery or an assisted reproduction treatment such as *in vitro* fertilisation

may be more appropriate. Medical treatment of pain caused by endometriosis is generally effective. There is little difference in efficacy between the different medications but their adverse effect profiles differ greatly. It appears that gonadotropin-releasing hormone agonists, particularly when used with add-back estrogen, may be more acceptable to women than other treatments. Laparoscopic surgical treatment of minimal and mild endometriosis has been demonstrated to increase fecundity. Surgical treatment has also been shown to decrease pain scores compared with expectant management.

Ongoing and future research examining the aetiology of endometriosis at the immunological and genetic levels should usher in new treatments directed at the actual cause of the disease. More randomised trials examining the role of surgery, and comparing surgical and medical treatments, are also required and are necessary if we are to continue in our attempts to adopt an evidence-based approach to treatment.

Endometriosis causes pain and infertility for millions of women worldwide. Although it was first reported by Rokitansky 140 years ago, debate continues over its aetiology, pathogenesis and treatment.

1. Aetiology

Estimates of the prevalence (proportion of women with the disease at any one time) and incidence (proportion of women developing the disease during 1 year) of endometriosis vary greatly, from 1 to 50% of reproductive-age women. This may be because of different patient populations sampled (e.g. fertile or infertile women) and because increasingly subtle forms of the disease are being recognised. Large studies suggest a prevalence of endometriosis of 0.5 to 5% in fertile and 25 to 40% in infertile women.[1-3]

Endometriosis may be defined as the presence and proliferation of endometrial tissue outside the uterine cavity. The most widely accepted theory of pathogenesis is Sampson's 'transplantation theory'.[4] Sampson proposed that retrograde flow of endometrial cells from the uterine cavity, through the Fallopian tubes, into the pelvic cavity during menstruation deposits viable tissue, which implant on the peritoneal surface. This theory is supported by data showing an increased occurrence of endometriosis in women with Mullerian duct anomalies resulting in an obstructed genital outflow tract and thus increased retrograde menstruation. Added to this are epidemiological data suggesting that women who menstruate more frequently, more heavily or for a longer duration, and therefore have increased exposure to retrograde menstruation, also have a higher risk of developing the disease.[5]

However, 90% of women have retrograde flow during menses but only 0.5 to 5% of reproductive-age women develop endometriosis.[6] These data suggest that normal women may have protective mechanisms whereby endometrial cells present in the peritoneal cavity are removed or in some way prevented from implanting and growing. Accordingly, women with endometriosis may have some deficiency in this regard.

However, other theories are needed to explain the occasional presence of endometriosis in sites distant from the female pelvis: for example, in the pleural cavity, central nervous system and, in a few reported cases, the male prostate. It has been proposed that lymphatic or haematogenous spread, metaplasia of peritoneal mesothelium, or the development of endometriosis from embryonic rests could explain these findings.[5] More recently, the idea of a composite theory, encompassing features of all of the above, has become attractive. However, it is probable that most endometriosis develops after retrograde menstruation and implantation of endometrial tissue in the pelvis.

It is increasingly recognised that immune sys-

tem factors are involved with the development and progression of endometriosis. The peritoneal fluid of affected women has altered levels of prostanoids, cytokines, growth factors and interleukins.[7] It is not clear, though, whether these differences cause or are caused by the disease process.

There appears to be a degree of genetic susceptibility. This is suggested by the observation of higher disease prevalence in first-degree relatives of affected women than in controls.[8] The Oxford Endometriosis Gene (OXEGENE) study, an international collaborative project involving over 50 centres, is attempting to identify susceptible loci for endometriosis genes. Once the genes involved are identified, analysis of the biochemical function of gene products may lead to a better understanding of the pathophysiology and aetiology of endometriosis.[8]

2. Pathophysiology

The two most common disorders associated with endometriosis are infertility and pain. However, endometriosis is something of an enigma. Many women who have disease discovered incidentally at surgery are fertile and do not have pelvic pain, and others have severe endometriosis with minimal symptoms.

In an attempt to aid in standardisation of diagnosis and analysis of disease severity, progression and response to treatment, staging systems have been developed. The most commonly used is that proposed by the American Society for Reproductive Medicine (ASRM).[9] Following visual assessment of the pelvis at surgery, a weighted score is calculated based on the number, size, position and depth of endometrial implants, and the presence and type of adhesions. Arbitrary cut-off values divide the disease into minimal, mild, moderate or severe grades (figs 1 and 2). Unfortunately, even though the classification system was designed to predict probability of pregnancy following treatment, prospective studies have failed to demonstrate a convincing relationship between disease stage and pregnancy outcome.[10] Similarly, endometriosis stage correlates poorly with severity of pain (although this was not the intention of the ASRM classification). This lack of correlation between disease grade and pain or pregnancy may result from a relative lack of understanding of the pathophysiology of endometriosis. As knowledge increases, increased numerical weighting may be given to the factors recognised to be of greater pathological importance, or new factors may have to be incorporated into the scheme.

The classic endometriotic implant is the blue-black 'powder-burn' lesion. More recently, endometriosis has been recognised to appear in many other, more subtle forms. These lesions may appear as red (red, red-pink and clear lesions) or white (white, yellow-brown and peritoneal defects) [fig. 3].[9] It is likely that the powder-burn lesions represent the end stage of endometriotic lesions. The varying appearances of endometriosis partly explain the varying prevalence and incidence estimates.

Endometriosis is thought to be a cause of infertility. This theory is based on observations of a higher prevalence of endometriosis in infertile than fertile women.[3] Although this does not prove causation, it is generally accepted that endometriosis severe enough to distort pelvic anatomy, affecting oocyte pick-up from the ovary, is associated with reduced fecundity. The effect of minimal and mild endometriosis on fertility is unclear. It has been suggested that such disease may interfere with fertility through raised levels of intrapelvic growth factors, which could affect the microenvironment within the Fallopian tube or the pelvis, thus affecting the oocytes in some way.[7] Additional support for this theory comes from cohort studies where women with peritoneal endometriosis undergoing artificial insemination had lower pregnancy rates than those with no endometriosis.[11] A recent randomised, controlled study examined the benefit of surgery in infertile women with minimal or mild endometriosis.[12] Treatment resulted in a significantly greater rate of ongoing pregnancy (>20 weeks gestation) than expectant management, implying that presence of disease reduces fecundity. However, the same research group also

Patient's name _____ Date _____

Stage I (minimal) 1-5
Stage II (mild) 6-15
Stage III (moderate) 16-40
Stage IV (severe) >40
Total _____

Laparoscopy_____ Laparotomy_____ Photography_____

Recommended treatment _____

_____

Prognosis _____

Peritoneum	**Endometriosis**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	Posterior culdesac obliteration	Partial		Complete
		4		40
Ovary	**Adhesions**	<1/3 enclosure	1/3-2/3 enclosure	>2/3 enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4•	8•	16
	L Filmy	1	2	4
	Dense	4•	8•	16

• If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R_____%, W_____% and B_____%. Total should equal 100%.

Additional endometriosis:_____

_____

_____

_____

Associated pathology:_____

_____

_____

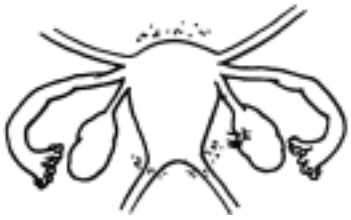
_____

To be used with normal tubes and ovaries

To be used with abnormal tubes and ovaries

Fig. 1. Scoring sheet for staging of endometriosis at laparoscopy using American Society for Reproductive Medicine revised classification.[9]

Stage I (minimal)



Peritoneum		
Superficial endo	1.3cm	2
R. ovary		
Superficial endo	<1cm	1
Filmy adhesions	<1/3	1
Total points		4

Stage II (mild)

Peritoneum		
Deep endo	>3cm	6
R. ovary		
Superficial endo	<1cm	1
Filmy adhesions	<1/3	1
L. ovary		
Superficial endo	<1cm	1
Total points		9

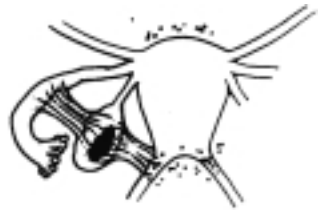
Stage III (moderate)

Peritoneum		
Deep endo	>3cm	6
Culdesac		
Partial obliteration		4
L. ovary		
Deep endo	1-3cm	16
Total points		26

Stage III (moderate)

Peritoneum		
Superficial endo	>3cm	4
R. tube		
Filmy adhesions	<1/3	1
R. ovary		
Filmy adhesions	<1/3	1
L. tube		
Filmy adhesions	<1	16•
L. ovary		
Deep endo	<1cm	4
Dense adhesions	<1/3	4
Total points		30

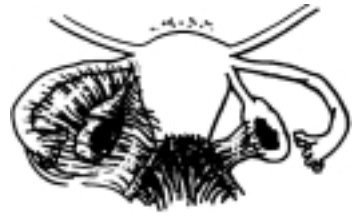
Stage IV (severe)



Peritoneum		
Superficial endo	>3cm	4
L. ovary		
Deep endo	1-3cm	32••
Dense adhesions	<1/3	8••
L. tube		
Dense adhesions	<1/3	8••
Total points		52

• Point assignment changed to 16 (fig. 1)
•• Point assignment doubled

Stage IV (severe)



Peritoneum		
Deep endo	>3cm	6
Culdesac		
Complete obliteration		40
R. ovary		
Deep endo	1-3cm	16
Dense adhesions	<1/3	4
L. tube		
Dense adhesions	>2/3	16
L. ovary		
Deep endo	1-3cm	16
Dense adhesions	>2/3	16
Total points		114

Fig. 2. Examples of stages of endometriosis (endo) using American Society for Reproductive Medicine revised classification.[9] In those patients with only one adnexa, points applied to disease of the remaining tube and ovary are doubled.

compared the patients managed expectantly with a group of women with unexplained infertility who had had a normal laparoscopy as part of the entry criteria for the randomised trial.[13] This prospective cohort study found that the cumulative probability of ongoing pregnancy during the 36 weeks following the diagnostic laparoscopy was similar between women with minimal or mild endometriosis and those with unexplained infertility. However, it is possible that endometriosis may be only a marker for a coexisting pathological process that is actually responsible for causing subfertility.

Endometriosis implants on the surface of the ovary can, ultimately, lead to invagination and the formation of an endometriotic cyst, known as an endometrioma. These cysts have a wall formed by

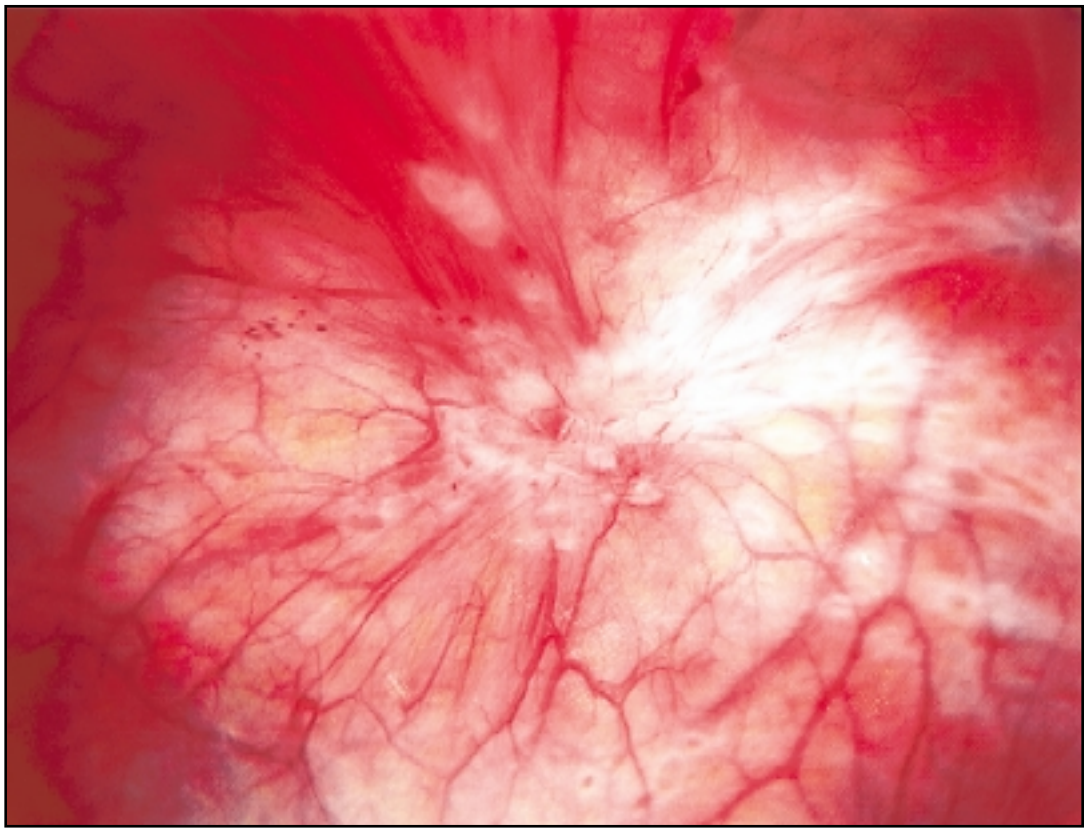


Fig. 3. A 'white' endometriotic lesion on the peritoneal surface. Note the peritoneal puckering and neovascularisation, with vessels drawn in towards the lesion (courtesy of Professor T. Tulandi, McGill University, Montreal, Canada).

endometriotic tissue and contain dark, thick cystic fluid; hence their other name, 'chocolate cysts'.

There is no universally accepted hypothesis on how endometriosis could result in pain. Pain may be caused by inflammatory factors produced by the endometrial glandular cells in response to the cycling hormones, and may also be the result of scarring or adhesions from longstanding disease. However, the role of adhesions in pelvic pain is disputed. Endometriomas could cause pain through a pressure effect during intercourse. Deep lesions, including those that invade the rectovaginal septum, appear to correlate with the severity of pelvic pain.[14] Such pain may be the result of nerve invasion in a similar manner to malignancy.

The natural history of endometriosis is not well understood, although the disease seems to progress in untreated women.[15] However, regression of disease in 30 to 40% of women on second-look laparoscopy is well recognised in the placebo arms of randomised trials.[16] However, it is unclear to what extent early treatment can slow or halt disease progression.

3. Symptoms

Although many women are asymptomatic, the classic complaint of endometriosis is pelvic pain. Women may complain of painful periods (dysmenorrhoea), the pain often starting a few days before

menstruation, and/or painful intercourse (dyspareunia), particularly on deep penetration and often persisting for hours afterwards. That the pain is generally cyclical results from the response of endometriotic tissue to the cycling reproductive hormones. As endometriosis worsens, the pain may become continuous. In addition pain may be experienced during defecation or micturition because of endometriosis affecting the rectum or bladder.

A difficulty in diagnosis is that pelvic pain is a common symptom in women without endometriosis. Many women and physicians may mistakenly consider the symptoms normal for menstruating women. In addition, there is considerable overlap with other conditions such as irritable bowel syndrome and pelvic inflammatory disease. A decision has to be made at what point a woman should undergo a surgical procedure, which carries some risk, in order to make a diagnosis.

4. Diagnosis

Endometriosis may be suggested by a number of signs on physical examination of the pelvis. There may be tenderness and nodularity at points of endometriotic deposits, particularly along the uterosacral ligaments (which help support the uterus). The uterus may be fixed and retroverted secondary to endometriosis and adhesion formation. The ovaries may be enlarged and tender secondary to endometriomas.

For diagnosis and staging of endometriosis a surgical procedure, generally a laparoscopy, is necessary to visualise disease implants. Laparoscopy involves CO_2 distension of the abdominal cavity and inspection of pelvic contents with a telescope inserted through a small incision near the umbilicus.[17] Two or more small incisions may be made for the insertion of other instruments when treatment is planned. Advantages of laparoscopy over laparotomy include shorter hospitalisation and recovery time. Occasionally, biopsy and histology of suspicious lesions is required. Surgical diagnosis also offers the option of treatment of lesions and/or adhesions at the same time (see section 5.2).

More recently, techniques such as ultrasonography or magnetic resonance imaging (MRI) have been used. Transvaginal ultrasound, which is routinely used in an infertility setting, is able to diagnose endometriotic cysts (endometriomas) within the ovaries. However, ultrasound is unable to see the more common superficial peritoneal disease. MRI may be a useful noninvasive tool in the diagnosis of deep endometriosis. Although it has limitations in the visualisation of small endometriotic implants and adhesions, it has the ability to characterise the lesions, to study extraperitoneal locations and the contents of pelvic masses.[18-20]

5. Treatment

The aim of treatment of endometriosis is to remove or diminish disease deposits. This may be attempted through medical or surgical means. It has long been recognised that endometriotic glands are hormonally sensitive. Following observations of the improvement of endometriosis symptoms during pregnancy and after the menopause, medical regimens have been developed to mimic these physiological states. A pseudopregnancy state can be induced with the use of the oral contraceptive pill[21] or continuous progestogens.[22] A pseudopostmenopausal state is created by inducing anovulatory, hypoestrogenism with drugs such as danazol, gonadotropin-releasing hormone (GnRH) agonists and progestogens. The aim of these treatments is to induce atrophy within the hormonally-dependent ectopic endometrium deposits so that they shrink in size and number. Two major problems with medical therapies are that, because of anovulation, conception is not possible during treatment and that treatment is prolonged, generally for 6 months. If pain is the only complaint, this is not important, but for subfertile women 6 months of iatrogenic infertility is generally unattractive. Management must be tailored according to whether infertility is an issue. If surgery is used, endometriotic deposits are fulgurated using diathermy or vaporised with laser.

The ideal study design to determine the effectiveness of a treatment modality, in order to mini-

mise bias, is a randomised, controlled trial (RCT). However, most therapies have been used on an empirical basis based on observational data. While RCTs offer a high level of evidence, the results of meta-analysis, in which suitable RCTs are combined, are considered to provide the highest evidence level (US agency for Healthcare Policy and Research). The Cochrane Collaboration (http://www.cochrane.org) is an international nonprofit organisation that aims to supply accurate up-to-date information about the effects of healthcare. The collaborative group has published a number of systematic, meta-analytic reviews examining the efficacy of treatment for endometriosis associated with pain or infertility and these, along with other published meta-analyses, are used where possible. We first review medical therapies, describing each drug class in turn, before summarising the use of medications in treating infertility or pain. Surgical treatment of endometriosis is then reviewed.

5.1 Medical Treatment

5.1.1 Progestogens

Progestogens taken continuously induce an anovulatory, hypoestrogenic state through suppression of pituitary gonadotropin release. Additionally, both normal and ectopic endometrium is decidualised. The presumed result is atrophy of endometriotic implants. This class of drug has been used for endometriosis treatment for more than 3 decades.[22] An advantage of progestogens compared with other medical treatments is that they tend to be cheaper and better tolerated, with fewer adverse effects.

The progestogen medroxyprogesterone (medroxyprogesterone acetate; MPA) can be administered either parenterally by intramuscular injection or orally. Common dosage regimens are 150mg intramuscularly every 3 months or 30 mg/day orally continuously for 90 days. Higher oral dosages of 50 to 100 mg/day appear to confer no benefit over the 30 mg/day dosage. Depot MPA may result in a prolonged period of anovulation following the last injection. This makes it unsuitable for women who may desire conception. Adverse effects of these MPA regimens include breakthrough bleeding (about 25% of women), bodyweight gain, depression and bloating. Other progestogens used in endometriosis treatment are dydrogesterone and megestrol (megestrol acetate).

5.1.2 Antiprogestogens

Antiprogestogens include gestrinone and mifepristone. Gestrinone has been examined in a number of studies and has a more established role in the treatment of endometriosis than mifepristone, a relatively new drug. Antiprogestogens inhibit ovulation, inducing a hypoestrogenic state, and so have a similar mode of treatment action for endometriosis to that of progestogens.

5.1.3 Danazol

Danazol is an isoxazole derivative of the synthetic steroid 17α-ethinyl testosterone. The drug has a complicated, multifactorial mode of action but the end result is anovulation with hypoestrogenism and hyperandrogenism. Danazol (and its metabolites) modestly suppresses pituitary gonadotropin secretion and, in particular, the luteinising hormone surge required for ovulation. It binds to both androgen and progesterone receptors, and inhibits various steroidogenic enzymes. One of the main adverse effects of danazol is hyperandrogenism, which results from its agonistic affinity for androgen receptors, its displacement of testosterone from sex hormone-binding globulin (SHBG) and its effect on decreasing the production of SHBG. It also appears to have immunosuppressive properties, including inhibition of lymphocyte proliferation *in vitro* and suppression of autoantibody production.[23] This is of interest with the recent demonstration of increased immune system activity both in the pelvis and systemically in patients with endometriosis.

Danazol was the first drug approved by the US Food and Drug Administration for the treatment of endometriosis and it remains widely prescribed. However, the androgenic adverse effects are particularly troubling for women. They include acne, oily hair and skin, bodyweight gain and lowering of the voice. The availability of other newer drugs

with fewer unpleasant effects has reduced the use of danazol.

5.1.4 Oral Contraceptives

Combined estrogen-progestogen oral contraceptives (OC) were introduced as treatment to create a pseudopregnancy state after the observation that endometriosis symptoms improve during pregnancy.[21] The doses originally used were high but have steadily declined over the decades. When taken on a daily basis, without a pill-free break, this treatment results in amenorrhoea, and the patient obviously does not have pain during menstruation.

5.1.5 Gonadotropin-Releasing Hormone Agonists

Long-acting GnRH agonists are synthetic derivatives of the decapeptide GnRH. Nafarelin, goserelin and triptorelin are decapeptides and buserelin, leuprorelin (leuprolide) and histrelin are nonapeptides. GnRH agonists have their effect by down-regulating hypothalamo-pituitary GnRH receptors, resulting in decreased gonadotropin secretion, ovarian quiescence and reduced serum estrogen levels. Nafarelin, leuprorelin and goserelin are the 3 GnRH agonists currently approved for treatment of endometriosis in the US. Nafarelin is delivered by topical absorption nasally twice daily, leuprorelin is available in a daily subcutaneous or monthly intramuscular preparation, and goserelin is administered as a slow sustained release implant.[23]

Adverse effects of GnRH agonist therapy are related to hypoestrogenism. In the short term there are menopausal symptoms such as hot flushes and vaginal dryness. Long term use is associated with a reduction in bone mineral density (which is generally reversible on treatment withdrawal) at the lumbar spine of $3.2 \pm 1.8\%$ from baseline at 24 weeks and $6.3 \pm 2.3\%$ at 52 weeks of continuous treatment.[24] This obviously precludes the use of long term GnRH agonist therapy and most regimens are for a maximum of 6 months. However, recent interest has centred on the use of 'add-back' sex-steroid hormones or other bone-sparing agents such as estrogens, progestogens or organic bisphosphonates to prevent or reduce bone density loss. Such an approach may increase the length of time that GnRH agonist can be administered.

A recent RCT randomised 201 women with endometriosis to 12 months of 4-weekly depot leuprorelin and 1 of 4 add-back groups.[24] Group A received placebo, group B norethindrone acetate (norethisterone) 5mg (a progestogen) and a placebo for estrogen, group C norethindrone and conjugated equine estrogens 0.625 mg/day, and group D norethindrone and estrogens 1.25 mg/day. By week 8, all 4 groups showed significant improvement in pelvic pain scores compared with baseline levels. Group A experienced a $6.3 \pm 2.3\%$ ($p \leq 0.001$) loss in bone density after 52 weeks, whereas bone density was preserved in all 3 add-back groups.[24]

Combined GnRH agonist with add-back estrogen is expensive compared with other endometriosis medications such as MPA.

5.1.6 Endometriosis-Related Infertility

Unless endometriosis is so severe that major distortion of the pelvic anatomy results, women with endometriosis are not completely infertile but may have a monthly conception rate below that of unaffected women. All of the medications discussed in section 5.1 cause anovulation and so reduce the monthly conception rate during treatment to zero. Therefore, if therapy is to be of value in treating infertility, the post-treatment conception rate needs to be significantly increased.

A systematic review examining ovulation suppression versus placebo or no treatment included 4 RCTs.[25] Ovulation suppression was achieved with danazol, MPA or gestrinone. No suitable trial examining the use of the OC against placebo/no treatment was available for inclusion. The common odds ratio for pregnancy following suppression versus placebo/no treatment was 0.83 [95% confidence interval (CI) 0.5 to 1.39]. Since the CIs cross unity, ovulation suppression has no beneficial effect on conception rates in women with endometriosis compared with rates in those receiving placebo or no treatment. On examining RCTs comparing MPA, OC, gestrinone or GnRH agonists with an 'active control' (danazol), no difference in fecundity was seen between groups. The common

odds ratio for pregnancy after use of these ovulation suppression agents compared with danazol was 1.20 (95% CI 0.85 to 1.68). In view of the lack of evidence of benefit of all of the medications described in the treatment of endometriosis-associated infertility, their use cannot be recommended. In addition, in view of the decrease in fecundity during the treatment period and the adverse effects of therapy, their use should be discouraged when infertility is the primary problem.

Although assisted reproductive technologies such as ovulation induction or *in vitro* fertilisation (IVF) do not treat endometriosis *per se*, they can successfully treat the associated infertility. An RCT compared superovulation using gonadotropins followed by intrauterine insemination (IUI) against no treatment for women with minimal or mild endometriosis.[26] The ovulation induction/IUI group had 14 live births out of 127 cycles (11%) compared with 4 out of 184 control cycles (2%). This gives an odds ratio for live birth of 5.6 (95% CI 1.8 to 17.4). Age-related pregnancy rates after 1 cycle of IVF are illustrated in figure 4 and should be kept in mind when discussing treatment options. In particular, the decrease in IVF success as the woman passes through her mid to late 30s must be considered.[27] If attempting surgical treatment, it is usually necessary to wait 6 to 12 months after surgery to assess success (conception) or failure. For an older woman, her chance of IVF success may have reduced significantly during that time and she may be better off moving straight to IVF.

The process of an IVF cycle is well described elsewhere.[28] Briefly, treatment involves down-regulation of the hypothalamo-pituitary-ovarian axis with GnRH agonist followed by gonadotropin ovarian stimulation. Gonadotropins may either be urinary or recombinant preparations. Once a multifollicular ovarian response is gained, oocytes are retrieved transvaginally under ultrasound guidance and fertilised *in vitro*, and subsequently multiple embryos are transferred to the uterine cavity.

A recent meta-analysis (not published in full) of published studies has suggested a lower pregnancy rate for women with endometriosis undergoing

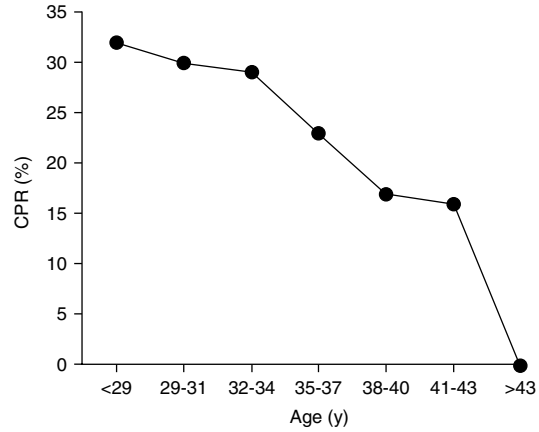


Fig. 4. Clinical pregnancy rate (CPR) per commenced *in vitro* fertilisation cycle (with female age). Data shown are 1500 consecutive cycles at the McGill Reproductive Center, 1996-1999.

IVF compared with women with tubal disease.[29] However, analysis of large databases indicates that there is no difference in outcome.[30,31] The presence of endometriosis in donor oocyte recipients, when the donated oocytes are from endometriosis-free women, has not been found to result in poorer outcomes than in donor oocyte recipients with no endometriosis.[32,33] This suggests that if endometriosis truly reduces implantation rates, this must be as a result of a negative effect on oocyte and embryo quality, rather than a local effect within the uterine cavity. Studies have demonstrated differences in the endocrine, paracrine and autocrine conditions induced during folliculogenesis in women with and without endometriosis, which could explain any lower oocyte and embryo quality.[34]

In a case-control study, the presence of ovarian endometriosis (i.e. moderate or severe endometriosis) was associated with a poorer ovarian response and a requirement for more ampoules of gonadotropins.[35] However, the cumulative pregnancy and live birth rates after 5 IVF cycles (62.6 and 50.9%, respectively) were similar to those in age-matched controls with normal ovaries and a diagnosis of tubal infertility.[35]

It appears that because a comparable number of embryos are available for transfer, even in patients with advanced disease, the outcome of IVF in terms of implantation and ongoing pregnancy rates is similar in patients with varying disease severity. The presence of endometriomas does not generally impair the results of IVF but it increases the risk of infection at the time of oocyte collection.[36] However, further large, prospective, controlled studies are required before a consensus can be reached on the effect of endometriosis on IVF outcome. More recently, women with endometriosis who have polycystic ovarian morphology may be considered for *in vitro* maturation treatment.[37] This involves immature oocyte aspiration from unstimulated ovaries, *in vitro* oocyte maturation and fertilisation, and multiple embryo transfer to the uterus.

5.1.7 Endometriosis-Related Pain

Ovulation suppression is the mainstay of medical treatment for endometriosis-related pain. The Cochrane Group has systematically analysed suitable RCTs involving the use of danazol, OC, progestogens, antiprogestogens and GnRH agonists in treating pain symptoms.[38-41]

A systematic review[38] identified 4 placebo-controlled trials examining the role of danazol in treating pain. In 2 of the trials danazol was used as an adjunct to surgery and in 2 it was used alone. Symptoms were improved in the danazol groups at the end of the 6-month treatment period and also after 6 months off therapy compared with placebo.[42,43] Laparoscopic scores were improved with danazol when compared with either placebo or no treatment. Adverse effects were more commonly reported in patients receiving danazol than placebo but patient satisfaction was greater in the active treatment group. The authors of the systematic review conclude that danazol is effective in treating the symptoms and signs of endometriosis but its use is limited by the occurrence of androgenic adverse effects.[38]

In a systematic review of the use of OC in endometriosis-related pain only 2 RCTs were identified.[41] One of these was excluded, as the OC preparation is no longer in use.[44] The remaining study compared 6 months' treatment with a cyclical low dose contraceptive pill (ethinyl estradiol 0.02mg with desogestrel 0.15mg) against a monthly subcutaneous injection of goserelin 3.6mg in 57 women.[45] Change in pain scores after 6 months' treatment and after 6 months' follow-up, and the occurrence of adverse effects were analysed. Goserelin was more effective at relieving dysmenorrhoea during treatment. This is explained by the amenorrhoea in the goserelin group but not the OC group. Six months after treatment, no woman had experienced complete resolution of dysmenorrhoea and neither treatment was better than the other. Goserelin was possibly more effective at relieving painful intercourse than the OC during treatment; however, at the end of treatment and after 6 months' follow-up there were no differences between the groups. In the treatment of nonmenstrual pain there were no significant differences in pain scores at the end of treatment between the groups. Six months after treatment, symptoms had recurred in all patients. Adverse effects of hot flushes, vaginal dryness and insomnia were more common in the goserelin group, whereas headaches and bodyweight gain were associated with OC use.

There is a shortage of good data on the use of the OC in treating endometriosis, even though the pill was one of the earlier treatments applied (although in much higher doses than today's preparations). The study described in the previous paragraph suggests that the OC is as good as GnRH agonists in treating nonmenstrual pain and painful intercourse. The frequency of the pill-free break, during which withdrawal bleeding occurs, can be reduced to 3-monthly or less. The effectiveness of the OC in treating dysmenorrhoea would then be expected to approach that of GnRH agonists. The troublesome adverse effects of GnRH agonists could be reduced with concurrent administration of estrogen, which may also allow the regimen to be continued for longer than 6 months. These changes may negate the applicability of previous studies, such as the one discussed. Further comparative studies are required.

The Cochrane analysis of the use of progestogens and antiprogestogens has recently been completed.[40] Seven suitable RCTs were identified: 3 of these examined progestogens and the other 4 the antiprogestogen gestrinone. Only 2 RCTs were identified that considered the role of progestogens alone in the treatment of symptomatic endometriosis.[46,47] The Overton study compared cyclical (luteal phase) therapy of 2 different doses of dydrogesterone versus placebo.[46] However, of a total of 62 patients randomised, 5 were excluded after randomisation (4 conceived) and 23 were lost to follow-up. Dydrogesterone was not shown to be superior to placebo in either symptom or ASRM score reduction. The other study compared depot MPA with a combination of low dose OC pill and danazol.[47] Both groups showed significant reductions from baseline symptoms. The progestogen appeared to be more effective in the reduction of dysmenorrhoea at 12 months.

The Cochrane group identified no RCTs comparing the antiprogestogen gestrinone with placebo or no treatment.[40] Two studies compared the efficacy of gestrinone with danazol[48,49] and one with the GnRH agonist leuprorelin.[50] There appears to be no difference in either objective or subjective efficacy between gestrinone and danazol. The androgenic adverse effects of greasy skin and hirsutism were more common in the gestrinone than the danazol group. Decreased breast size, muscle cramps and hunger were more common in the danazol group. Both gestrinone and the GnRH agonist leuprorelin reduced symptoms compared with baseline values.[50]

A further systematic review has reported on GnRH agonists for the treatment of endometriosis-related pain.[39] 26 RCTs were included in the review. Only one compared the GnRH agonists with placebo and there were no trials comparing GnRH agonists with progestogens or surgery. 15 compared GnRH agonists with danazol, the 'gold standard' treatment prior to the introduction of GnRH agonists. In 24 of the 26 trials, treatment was given for 6 months. There appeared to be little or no difference in the effectiveness of GnRH agonists compared with other medical treatments for endometriosis such as danazol, OC or gestrinone. The addition of add-back therapy did not affect the efficacy scores but resulted in significantly fewer hot flushes and preservation of bone mineral density.[24]

In summary, there appear to be few if any differences in the effectiveness of the different medical treatments in treating endometriosis-related pain (table I). Danazol and GnRH agonists have proven efficacy. The majority of trials involving the other drugs are randomised comparisons against danazol or GnRH agonists. Since they appear no better or worse than danazol or GnRH agonists, by extrapolation we can conclude they are also effective treatments. Differences relate to the adverse effect profiles. It appears that GnRH agonists may be more acceptable to women than other treatments, particularly when add-back therapy is given. Further research is required to compare GnRH agonists with treatments such as the OC, MPA and surgical ablation. The most suitable regimen of add-back therapy with a GnRH agonist is not yet established.

5.2 Surgical Treatment

Surgery can be either conservative or radical. The aim of conservative treatment is to destroy endometriotic implants, remove endometriomas and divide adhesions so as to restore the pelvis to as near normal as possible. Ideally such surgery is performed laparoscopically; however, laparotomy may have to be performed for removal of large endometriomas with extensive pelvic adhesions, when bowel involvement is severe, or in the absence of suitable equipment or surgeons with adequate laparoscopic training. Radical surgery involves removal of the uterus and/or ovaries. Assessment of the reproductive aims of the woman is important when planning treatment, as therapeutic options differ between a woman who has completed her family and another who has not.

5.2.1 Endometriosis-Related Infertility

The majority of reported studies are not randomised and controlled, but are retrospective

Table I. Summary of efficacy of medical and surgical treatments of endometriosis-associated pelvic pain and infertility

Infertility	
Medical treatment[a]	These therapies cause anovulation and reduce monthly fecundity. Their use cannot be recommended when infertility is the primary problem[25]
Assisted conception	*In vitro* fertilisation gives the highest chance of pregnancy for infertile women with endometriosis
Surgical treatment	Laparoscopic treatment of minimal and mild endometriosis increases fecundity.[12] The role of surgery in moderate or severe endometriosis is unclear
Pelvic pain	
Medical treatment[a]	Medical therapies are generally equally effective in reducing pain scores but differ greatly in adverse effect profiles[38-41]
Surgical treatment	Laparoscopic treatment of all grades of endometriosis reduces pain scores.[51,52] Whether medical or surgical treatment has greater efficacy is currently unclear

a Medical treatments include progestogens, antiprogestogens, danazol, oral contraceptives and gonadotropin-releasing hormone agonists.

and/or observational, with all the biases inherent in such a design. Without knowing the effect on fecundity of no treatment in a control group, few concrete conclusions can be drawn. Unless severe disease has totally distorted the pelvis, most women with endometriosis are not infertile but continue to have a monthly conception rate. Consequently, expectant management could give fertility results similar to or even better than those with surgery, particularly if the latter is destructive in nature.

However, a recent prospective, multicentre, double-blind, RCT examined the efficacy of surgical treatment of minimal and mild endometriosis on infertility.[12] 341 women were randomised and followed up for 36 weeks. The cumulative probability of pregnancy in the surgically-treated versus nontreated group was 30.7 and 17.7%, respectively (rate ratio 1.7; 95% CI 1.2 to 2.6). The fecundity rates per 100 person-months were 4.7 and 2.4 (rate ratio 1.9; 95% CI 1.2 to 3.1). The implants and adhesions were treated with diathermy, laser or a combination of the two. However, shortcomings of this study are that the patients were informed of the randomisation, approximately 10% of the women in each group received fertility medication or adhesiolysis, and the pregnancy rates in the control group were lower than expected.

There is a lack of RCTs examining the role of surgery in fertility patients with moderate or severe endometriosis. It is generally considered that attempting to correct anatomic defects surgically should result in better outcomes than medical treatment or expectant management.[53] However, this hypothesis has never been adequately tested.

It is recognised that the medical treatment of endometriomas is ineffective. The value of surgical treatment of endometriomas compared with medical or expectant management for fertility has not been tested in RCTs. Conception rates of about 50% by 3 years after treatment, whether by laparoscopy or laparotomy, are reported.[54] Of course, without an untreated control group, we are unaware what the rate would have been with expectant management.

In summary, it is clear that for infertile patients with endometriosis treatment options should include surgery. Medical treatments do not appear to increase fecundity. At some point many couples should be offered IVF treatment, as this gives the greatest chance of conception (table I).

5.2.2 Endometriosis-Related Pain

The majority of studies examining the role of surgery in pain treatment are nonrandomised and uncontrolled. Fortunately, a prospective, double-blind, RCT comparing laparoscopic laser treatment of all stages of endometriosis against no treatment has been reported.[51] 74 women were randomised. Six months after surgery 62.5% of treated, compared with 22.6% of untreated, women reported improvement or resolution of symptoms (fig. 5). Unfortunately, the surgical intervention included laser vaporisation of deposits and laparoscopic uterine nerve ablation as required. Conse-

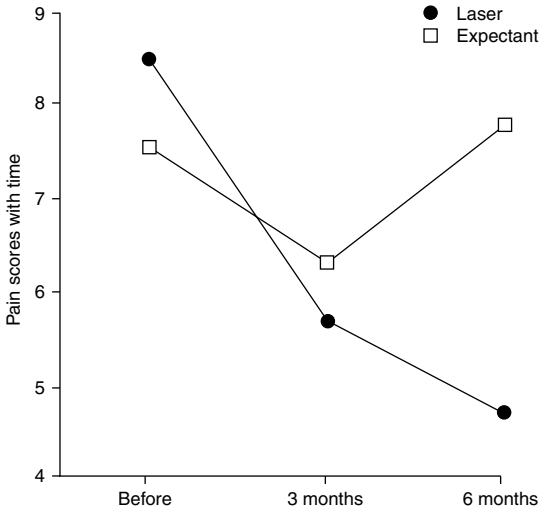


Fig. 5. Median visual analogue pain scores (with time) for women having either laser or expectant management of endometriosis diagnosed at laparoscopy.[51] The difference in pain scores between the 2 groups at 6 months after surgery was significant (p = 0.01).[51]

quently, it is not clear what the relative contribution of either of these laser techniques to the pain reduction was.

The Cochrane group has recently completed a systematic review of the surgical interruption of pelvic nerve pathways for dysmenorrhoea (including dysmenorrhoea due to endometriosis).[52] They identified 2 studies (1 not yet published) comparing uterine nerve ablation with routine endometriosis deposit ablation versus deposit ablation only. Combined treatment was no more effective in reducing pain than deposit ablation alone and, therefore, can not be recommended. Uterine nerve ablation is not without risk, as blood vessels and ureters run very close to the ligaments, and deaths have been reported.

Deeply infiltrating endometriosis can be associated with severe pain and difficult surgical excision. Again, no RCTs have been reported but large observational series suggest a cure rate for pelvic pain of 70% and a recurrence rate of 5% at 5 years.[55] If disease is infiltrating the rectovaginal septum, the recurrence rate may be higher.[56]

The relationship between adhesions and pain is unclear. A retrospective review of 100 consecutive laparoscopies for chronic pelvic pain and 88 for infertility did not find a significant difference in the density or the location of adhesions between the groups.[57] Again, studies examining the role of treatment are retrospective or observational rather than randomised and controlled. Two observational, uncontrolled studies suggest an improvement rate of 67 to 84% in pain after adhesiolysis.[58,59] However, adhesion reformation has been observed in 97.1% of patients and at 66% of the sites of the original adhesiolysis.[60]

Radical surgery in the form of a hysterectomy and bilateral salpingo-oophorectomy may result in pain relief in up to 90% of patients. Obviously the patient will be infertile afterwards, so the decision to proceed must not be taken lightly. It may be an appropriate procedure for older women or those who have completed their family. However, there is still the potential for pain resulting from residual endometriosis, adhesion formation or the ovarian remnant syndrome.

6. Conclusion

Endometriosis is a common condition affecting millions of women worldwide. Although much remains to be understood about the aetiology and pathophysiology of the condition, researchers are now examining the disease at the immunological and genetic levels. The insights gained should usher in new treatments directed at the actual cause of the disease. Although the majority of treatments used are not new, it is only fairly recently that RCTs of both medical and surgical therapies have been undertaken. More trials are needed, particularly in assessing the role of surgery, and in comparing surgical and medical treatment modalities. Such trials are necessary if we are to continue in our attempts to adopt an evidence-based approach to disease management.

References

1. Haupt BJ. Utilization of short-stay hospitals: annual summary for the United States, 1980. Vital Health Stat 1982; 13: 1-60
2. Houston DE, Noller KL, Melton LJ 3rd, et al. Incidence of pelvic endometriosis in Rochester, Minnesota, 1970-1979. Am J Epidemiol 1987; 125: 959-69
3. Strathy JH, Molgaard CA, Coulam CB, et al. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. Fertil Steril 1982; 38: 667-75
4. Sampson JA. Benign and malignant endometrial implants in the peritoneal cavity and their relation to certain ovarian tumours. Surg Gynecol Obstet 1924; 38: 287-311
5. Rock JA, Markham SM. Pathogenesis of endometriosis. Lancet 1992; 340: 1264-7
6. Halme J, Hammond MG, Hulka JF, et al. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984; 64: 151-4
7. Kim JG, Suh CS, Kim SH, et al. Insulin-like growth factors (IGFs), IGF-binding proteins (IGFBPs), and IGFBP-3 protease activity in the peritoneal fluid of patients with and without endometriosis. Fertil Steril 2000; 73: 996-1000
8. Kennedy S. The genetics of endometriosis. J Reprod Med 1998; 43: 263-8
9. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997; 67: 817-21
10. Guzick DS, Silliman NP, Adamson GD, et al. Prediction of pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis: 1996. Fertil Steril 1997; 67: 822-9
11. Omland AK, Tanbo T, Dale PO, et al. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod 1998; 13: 2602-5
12. Marcoux S, Maheux R, Berube S, et al. Laparoscopic surgery in infertile women with minimal or mild endometriosis. N Engl J Med 1997; 337: 217-22
13. Berube S, Marcoux S, Langevin M, et al. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. Fertil Steril 1998; 69: 1034-41
14. Cornillie FJ, Oosterlynck D, Lauweryns J, et al. Deeply infiltrating pelvic endometriosis: histology and clinical significance. Fertil Steril 1993; 53: 978-83
15. Redwine DB. Age related evolution in color appearance of endometriosis. Fertil Steril 1987; 48: 1062-3
16. Harrison RF, Barry-Kinsella C. Efficacy of medroxyprogesterone treatment in infertile women with endometriosis: a prospective, randomized, placebo-controlled study. Fertil Steril 2000; 74: 24-30
17. Tulandi T, editor. Atlas of laparoscopic and hysteroscopic techniques for the gynecologist. London: WB Saunders, 1999
18. Manfredi R, Valentini AL. Magnetic resonance imaging of pelvic endometriosis. Rays 1998; 23: 702-8
19. Kinkel K, Chapron C, Balleyguier C, et al. Magnetic resonance imaging characteristics of deep endometriosis. Hum Reprod 1999; 14: 1080-6
20. The investigation and management of endometriosis. Royal College of Obstetricians and Gynaecologists Guideline No. 24. London: RCOG, 2000
21. Kistner RW. Treatment of endometriosis by inducing pseudopregnancy with ovarian hormones. Fertil Steril 1959; 10: 539-54
22. Kistner RW. The use of newer progestins in the treatment of endometriosis. Am J Obstet Gynecol 1958; 75: 264-78
23. Lessey BA. Medical management of endometriosis and infertility. Fertil Steril 2000; 73: 1089-96
24. Hornstein MD, Surrey ES, Weisberg GW, et al. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Obstet Gynecol 1998; 91: 16-24
25. Hughes E, Fedorkow D, Collins J, et al. Ovulation suppression for endometriosis (Cochrane review). In: The Cochrane Library 2000; 1. Oxford: Update Software
26. Tummin IS, Asher LJ, Martin JSB, et al. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 1997; 68: 8-12
27. Tan SL, Maconochie N, Doyle P, et al. Cumulative conception and livebirth rates after in-vitro fertilization with, and without, the long, short and ultrashort regimens of the luteinising hormone releasing hormone agonist, buserelin. Am J Obstet Gynecol 1994; 171: 513-20
28. Tan SL, Kingsland C, Campbell S, et al. The long protocol of administration of luteinising hormone releasing hormone analogue is superior to the short protocol for ovarian stimulation for in-vitro fertilization. Fertil Steril 1992; 57: 810-4
29. Barnhart KT, Dunsmoor R, Coutifaris C. The effect of endometriosis on IVF outcome [abstract O-203]. Fertil Steril 2000; 74 Suppl. 1: S76
30. Tan SL, Royston P, Campbell S, et al. Cumulative conception and live birth rates after in vitro fertilisation. Lancet 1992; 339: 1390-4
31. Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 1996; 348: 1402-6
32. Sung L, Mukherjee T, Takeshige T, et al. Endometriosis is not detrimental to embryo implantation in oocyte recipients. J Assist Reprod Genet 1997; 14: 152-6
33. Diaz I, Navarro J, Blasco L, et al. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. Fertil Steril 2000; 74: 31-4
34. Garrido N, Navarro J, Remohi J, et al. Follicular hormonal environment and embryo quality in women with endometriosis. Hum Reprod Update 2000; 6: 67-74
35. Al-Azemi M, Lopez Bernal A, Steele J, et al. Ovarian response to repeated controlled stimulation in –in-vitro fertilization cycles in patients with ovarian endometriosis. Hum Reprod 2000; 15: 72-5
36. Gulekli B, Buckett WM, Tan SL. Stages of endometriosis: does it affect the success of IVF? In: Ben-Rafael Z, Shoham Z, editors. Controversies in obstetrics, gynecology and infertility. Bologna: Monduzzi Editore, 1999: 83-5
37. Chian RC, Gulekli B, Buckett WM, et al. Priming with human chorionic gonadotropin before retrieval of immature oocytes in women with infertility due to the polycystic ovary syndrome. N Engl J Med 1999; 341: 1624-6
38. Selak V, Farquhar C, Prentice A, et al. Danazol for pelvic pain associated with endometriosis (Cochrane review). In: The Cochrane Library 2000; 1. Oxford: Update Software
39. Prentice A, Deary AJ, Goldbeck-Wood S, et al. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis (Cochrane review). In: The Cochrane Library 2000; 1. Oxford: Update Software
40. Prentice A, Deary AJ, Bland E. Progestagens and anti-progestagens for pain associated with endometriosis (Cochrane review). In: The Cochrane Library 2000; 2. Oxford: Update Software
41. Moore J, Kennedy S, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis (Cochrane

review). In: The Cochrane Library 2000; 1. Oxford: Update Software
42. Telimaa S, Puolakka J, Ronnberg L, et al. Placebo-controlled comparison of danazol and medroxyprogesterone acetate in the treatment of endometriosis. Gynecol Endocrinol 1987; 1: 13-23
43. Telimaa S, Ronnberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis after conservative surgery. Gynecol Endocrinol 1987; 1: 363-71
44. Fedele L, Arcaini L, Bianchi S, et al. Comparison of cyproterone acetate and danazol in the treatment of pelvic pain associated with endometriosis. Obstet Gynecol 1989; 73: 1000-4
45. Vercellini P, Trespidi L, Colombo A, et al. A gonadotrophin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993; 60: 75-9
46. Overton CE, Lindsay PC, Johal B. A randomised, double-blind, placebo controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosis. Fertil Steril 1994; 62: 701-7
47. Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol 1996; 175: 396-401
48. Fedele L, Arcaini L, Bianchi S, et al. Gestrinone versus danazol in the treatment of endometriosis. Fertil Steril 1989; 51: 781-5
49. Bromham DR, Booker MW, Rose GL, et al. A multicentre comparative study of gestrinone and danazol in the treatment of endometriosis. J Obstet Gynaecol 1995; 15: 188-94
50. The Gestrinone Italian Study Group. Gestrinone versus a gonadotropin releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomised, double-blind study. Fertil Steril 1996; 66: 911-9
51. Sutton CJG, Ewen SP, Whitelaw N, et al. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil Steril 1994; 62: 696-700
52. Wilson ML, Farquhar CM, Sinclair OJ, et al. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea (Cochrane review). In: The Cochrane Library 2000; 2. Oxford: Update Software
53. Adamson GD, Pasta DJ. Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. Am J Obstet Gynecol 1994; 171: 1488-505
54. Adamson GD, Subak LL, Pasta DJ, et al. Comparison of CO_2 laser laparoscopy with laparotomy for treatment of endometriomata. Fertil Steril 1992; 57: 965-73
55. Koninckx PR, Martin D. Treatment of deeply infiltrating endometriosis. Curr Opin Obstet Gynecol 1994; 6: 231-41
56. Donnez J, Nisolle M, Casanas-Roux F, et al. Rectovaginal septum endometriosis or adenomyosis: Laparoscopic management in a series of 231 patients. Hum Reprod 1995; 10: 630-5
57. Rapkin AJ. Adhesions and pelvic pain: a retrospective study. Obstet Gynecol 1986; 68: 13-5
58. Daniell JF. Laparoscopic enterolysis for chronic abdominal pain. J Gynecol Surg 1989; 5: 61-6
59. Sutton C, Macdonald R. Laser laparoscopic adhesiolysis. J Gynecol Surg 1990; 6: 155-9
60. Operative Laparoscopy Study Group. Post-operative adhesion development following operative laparoscopy: evaluation at early second-look procedures. Fertil Steril 1991; 55: 700-4

Correspondence and offprints: Dr *Tim J. Child*, 25 Mill Lane, Oxford OX3 0QB, UK.
E-mail: timothychild@yahoo.com