

## Endometriosis: a new approach to an old disease – and new opportunities

**Around 10-15% of women of reproductive age are affected by endometriosis, but a lack of awareness surrounding it – possibly due to its non-life-threatening nature – means it has to date been rather a missed opportunity. The current diagnosis and treatment of this overlooked disease, and the future market potential, is described in this article by Cambridge Consultants senior research analyst Adam Guy**

Endometriosis often results in incapacitating pain as well as causing an estimated 35% of female infertility cases. Despite the potentially huge market opportunity for treatment, endometriosis has suffered from a chronic lack of investment, meaning it is poorly understood, challenging to diagnose and difficult to treat.

Patient groups have been lobbying hard over the last few years to increase awareness, and their efforts are gaining momentum. This, and recent advances in understanding, have made it an area that is ripe for breakthroughs in diagnosis and treatment.

Endometriosis is a chronic disease in which functioning tissue from the lining of the womb – the endometrium – is present outside the uterine cavity. This tissue continues to respond to the menstrual cycle leading to gradual fibrin deposition, adhesion formation and scarring in the abdominal cavity. This causes pain, both chronic and on a monthly basis, as well as leading to infertility in some cases. Figures vary, but it is estimated that some 5-25% of hospital admissions for female pelvic pain are due to endometriosis, in addition to countless lost working days. Based on a survey of over 7,000 women, the UK-based patient group Endometriosis UK has estimated the annual cost of endometriosis to industry and commerce at up to €30bn (\$40.5bn) in the EU alone.

Endometriosis has no cure and is a progressive disease that gradually comes to cover many of the vital organs, such as the bowel, making treatment difficult. Diagnosis is based on clinical symptoms, such as pain and infertility, confirmed by direct visualisation and biopsy of the endometriosis in a laparoscopic procedure. Treatments are essentially hormonal or surgical, with hormonal treatments aiming to suppress ovarian function to arrest the growth and activity of the endometriosis, and surgical treatments aiming to remove visible areas of endometriosis and restore anatomy by dividing scarring and adhesions. Hormonal treatments have good success rates, but can result in significant side effects, including effects that are similar to the menopause and de-feminising side effects.

Most crucially, whilst hormonal treatments may be able to halt progression of the disease, they are not able to improve

fertility. In fact, hormonal treatments stop ovulation completely.

In contrast to pharmaceutical treatments, surgery does improve fertility in moderate to severe cases, and may improve fertility in minimal to mild cases. It also offers good initial symptomatic relief, but is necessarily costly and around 45% of patients experience a return of their symptoms in the year that follows the surgery. Surgical treatment is frequently laparoscopic, although in some cases a laparotomy may be required. Surgical resection and ablation are then carried out to remove as much of the endometriosis as possible, typically assisted with CO<sub>2</sub>, Argon or Nd:YAG lasers. Ultimately, a total hysterectomy may be required, but this is only applicable for women with intractable pain who have completed child-bearing.

Currently, even the cause of endometriosis is uncertain. There are several competing theories, the most widely quoted of which dates back to 1927, where the disease was thought to be the result of retrograde transmission of endometrial tissue through the fallopian tubes into the abdominal cavity. This is possible because there is a small gap between the ovaries and the fallopian tubes. However, more recent work has proposed that it results from cells migrating throughout the body, or indeed, the endometrial tissue may have formed in the abdominal cavity even before birth. There is no definitive evidence in any direction, but there does appear to be a genetic predisposition to the disease. As a further complication, the amount and character of pain experienced does not appear to be correlated with the extent of disease found.

Achieving diagnosis is a major factor in this market, with an average time to diagnosis from onset of pain of around 10 years. This is partially due to the fact that many women and healthcare professionals are unaware of the condition, believing that painful periods are simply part of being female. This leads to misdiagnosis, or treatment simply with painkillers.

Lobby groups are fighting to increase awareness, including the leading of US Congress to pass a resolution on raising endometriosis awareness at the end of 2002. Individual US states have also been passing resolutions on classifying the

month of March as "Endometriosis Awareness Month". Irrespective of whether this ever happens, these are nevertheless critical steps towards raising awareness at US policymaker level. In the UK, a 13,000 strong petition was handed in to the Prime Minister in March 2006, calling for greater funding and improved awareness.

The difficulty in diagnosing and treating this condition is not surprising given the paltry research funding in this area. Only \$12m was spent by the US National Institutes of Health (NIH) in 2006 on endometriosis research in the US. This contrasts with spend on other chronic conditions, such as \$283m in research funding for asthma, and \$643m for Alzheimer's disease (see table over), and is a tiny fraction of the \$5.6bn spent on cancer research. The NIH annual expenditure equates to around 90 cents per endometriosis patient, whilst Alzheimer's disease funding equates to around \$160 per patient. Similarly, the total UK Medical Research Council (MRC) direct

funding of endometriosis research for the UK in 2001 was a mere £70,000 (around \$150,000). Corporate, rather than state, research funding is more difficult to assess, but a relatively limited product pipeline indicates limited investment. This is perhaps surprising, given that it has been estimated that the global market for pharmaceutical treatments alone will reach \$2.2bn by 2014 (Source: Datamonitor 2004).

Despite the lack of investment in fundamental research, new treatments are emerging, both pharmaceutical and surgical. There are currently three compounds pre-registered or in phase III trials, and a further three in phase II trials. Whilst these compounds are expected to give an improved side-effect profile, they are not expected to remove the need for surgery, particularly in the crucial case of improving fertility prospects.

A recent surgical advance is the Helica thermal coagulator. This device forms a plasma at the tip of a probe, which produces heating that is highly surface targeted. It is able to ablate very thin layers, down to a single layer of cells, making it ideal for treating endometriosis since the endometrial cells that need to be destroyed are often coating vital structures. The ability to ablate such thin layers in a controlled fashion allows treatment whilst sparing vital structures. The underlying technology is similar to argon beam coagulators from companies such as Valleylab, but is interesting in being solely targeted at the endometriosis treatment market. Helica has proved its technical competence in its native Scotland, and is now located in 45 hospitals across the UK. It was

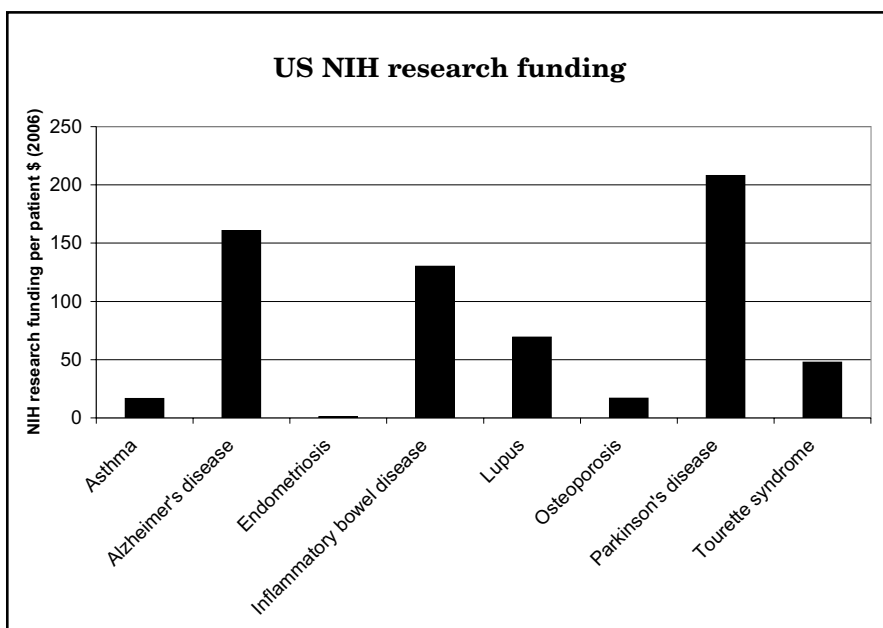
bought by Cytoc in 2006 with a view to global launch of a second-generation product in 2008.

The research that is being conducted is bringing to light possible new ways of targeting the disease. In 2004, a US team working with rats showed that endometrial tissue transplanted into the abdomen grew its own nerve supply that could then transmit information on injury and pain to the brain. In 2006, a team of Belgian scientists reported that local control of iron levels could provide a targeted treatment opportunity based on experiments in a mouse model.

The work in this area shows that radical advances in the treatment and management of endometriosis are possible, but have been held back by a continuing low level of awareness, which has led to difficulty in diagnosis and treatment, which in turn has led to low investment. Based on this analysis, perhaps the most significant advance that could break open

this market would be a noninvasive and inexpensive diagnostic. This would remove the need for an expensive and invasive laparoscopic procedure to achieve diagnosis, and create the awareness that would lead to a significant market pull for treatment.

Work in the area of non-invasive diagnostics is being conducted, and the emerging field of molecular imaging (see Clinica No 1238,



pp 10-12) may provide the solution. US researchers at the Garden State Cancer Center in New Jersey have identified a marker that is expressed in around 90% of endometriosis specimens, but weakly or not at all in normal endometrium. This marker can be targeted by a labelled monoclonal antibody, which is then used as a radioimmunoimaging agent. Being able to successfully target the disease for diagnosis also opens up the possibility of molecularly targeted treatments.

Emerging treatments and improvements in the fundamental understanding of the disease offer new hope for sufferers, but perhaps the greatest strides that need to be made are in diagnostics. Coupled with the inherent market potential, this increase in awareness should drive breakthrough products that will benefit patients, healthcare companies and society as a whole.

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