At last -- a quick and accurate way of diagnosing endometriosis

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A quick and accurate test for endometriosis that does not require surgery has been developed by researchers from Australia, Jordan and Belgium, according to new research published online today (Wednesday 19 August) in Europe's leading reproductive medicine journal *Human Reproduction*[1].

Until now there has been no way of accurately diagnosing endometriosis apart from laparoscopy - an invasive surgical procedure - and this often leads to women waiting for years in pain and discomfort before their condition is identified correctly and treated.

Now researchers at the University of Sydney and Mu'tah University in Karak, Jordan, have discovered that if they take a small sample of the endometrium (the lining of the uterus), which can be done by inserting the device for taking the biopsy via the vagina, and then test for the presence of nerve fibres in the sample, they can diagnose whether or not endometriosis is present with nearly 100% accuracy.

Endometriosis, which has been estimated to affect 10-15% of women of reproductive age, is a chronic gynaecological disease in which cells from the endometrium establish themselves outside the uterus, within a woman's pelvic area. Symptoms associated with it include infertility, painful periods, pelvic pain and pain during sexual intercourse. Once laparoscopy has identified endometriosis as the cause of these symptoms, treatment involves surgical removal (usually via laparoscopy) of the abnormally sited endometrial cells. However, laparoscopy itself

can be associated with complications and can adversely affect fertility in women who do not have endometriosis.

In a separate study also published online today in Human Reproduction, another research group from Belgium and Hungary has found that the density of nerve fibres in the endometrium was about 14 times higher in women with endometriosis than in healthy women, and that using specific markers to identify the presence of nerve fibres could predict with nearly 100% accuracy the presence of minimal to mild endometriosis [2].

In the first study, led by Professor Ian S. Fraser, head of the Queen Elizabeth II Research Institute for Mothers and Infants at the University of Sydney and Dr Moamar Al-Jefout, assistant professor in reproductive medicine at Mu'tah University, researchers took endometrial biopsies from 99 women who had consulted doctors about pelvic pain, infertility or both and who were undergoing laparoscopy for the condition.

The results from the endometrial biopsies were compared with the results of the laparoscopies, and the researchers found that in 64 women who had endometriosis confirmed by laparoscopy, all but one tested positive for the presence of nerve fibres in the endometrial biopsy. In the 35 women who were found not to have endometriosis by laparoscopy, no nerve fibres were found in 29 of the endometrial biopsies. In the other six cases, the biopsy found there were nerve fibres present; three of these women had severely painful periods and painful sex, and also a history of infertility, and of the other three, one had adhesions that were considered too slight to be endometriosis, while the other had a previous history of endometriosis.

Women with endometriosis and painful symptoms had significantly higher nerve fibre density in comparison with women with infertility but no pain (2.3 nerve fibres per mm2 compared to 0.8 per mm2

respectively). The mean average of nerve fibre density in the women with a laparoscopic diagnosis of endometriosis was 2.7 per mm2.

The study showed that testing endometrial biopsies for the presence of nerve fibres was able to diagnose endometriosis with 83% specificity (the proportion of negative cases of endometriosis correctly identified) and 98% sensitivity (proportion of positive cases correctly identified). This double blind study confirmed the results of a pilot study published in 2007 by the same group [3].

Dr Al-Jefout said: "This study has shown that testing for nerve fibres in endometrial biopsies is a valid and highly accurate diagnostic test for endometriosis. This test is probably as accurate as assessment via laparoscopy, the current gold standard, especially as it is unclear how often endometriosis is overlooked, even by experienced gynaecologists. Endometrial biopsy is clearly less invasive than laparoscopy, and this test could help to reduce the current lengthy delay in diagnosis of the condition, as well as allowing more effective planning for formal surgical or long-term medical management. It may be particularly helpful in cases of infertility."

Currently, diagnosing endometriosis via laparoscopy involves the woman being booked into hospital for the surgical procedure, an anaesthetic, and the presence of doctors, nurses and expensive equipment. In some countries there are long waiting lists for operations. In contrast, taking an endometrial biopsy is relatively quick and easy to organise and perform, and results are available within about three days. However, Dr Al-Jefout said: "It needs to be emphasised that this test requires a carefully collected endometrial biopsy and an experienced immunohistochemical pathology laboratory to confirm or exclude the presence of nerve fibres."

He continued: "Our results indicate that a negative endometrial biopsy result would miss endometriosis in only one percent of women.

Performing a planned laparoscopy only on a woman with a positive endometrial biopsy result would result in endometriosis being confirmed in eighty to ninety percent of these women. Thus, using this diagnostic test in an infertility workup would significantly reduce the number of laparoscopies performed without reducing the number of women whose endometriosis is diagnosed and surgically treated."

In addition, he said it could be particularly useful in teenagers with spasmodic symptoms but a family history of endometriosis. "The usual diagnostic delay in this special group is greater than in older women. An endometrial biopsy to confirm or exclude the diagnosis of endometriosis will help initiating earlier treatment and possibly preventing the progress of endometriosis, thus improving life style and protecting their future fertility."

The researchers plan to continue using the test in patients and to search for other markers to help refine the test further. "Ideally, we would like to develop a blood test as an even simpler means of providing early information on the presence or absence of endometriosis in order to assist doctors in early diagnosis. However, this endometrial biopsy test has proven so effective that it is currently the only test which appears to have equivalent efficacy to a diagnostic laparoscopy carried out by an experienced gynaecologist," he concluded.

In the second study, led by Professor Thomas D'Hooghe, coordinator of the University of Leuven Fertility Centre (Belgium), researchers looked at 40 endometrial samples, half taken from women with minimal to mild endometriosis diagnosed by laparoscopy and histology (microscopic examination of tissue), and half from women without the condition. They analysed the tissues for several markers indicating the presence of four types of nerve fibres (sensory C, Að, adrenergic and cholinergic nerve fibres).

Dr Attila Bokor, a doctoral fellow at the University of Leuven, who did the study as part of his PhD project said: "We observed nerve fibres in the endometrial samples of ninety percent (18 out of 20) of the women with endometriosis. The density varied throughout the samples, with few specimens showing counts above 30 per mm2, and with most between 0 and 10 per mm2. None, or very few, nerve fibres, were detected in any of the samples from women without endometriosis. The density of the small nerve fibres was about 14 times higher in endometrium from patients with minimal to mild endometriosis when compared with women with a normal pelvis."

Prof D'Hooghe said: "Our data show that the combination of three different neural markers increases the sensitivity, specificity and diagnostic accuracy of this method of testing for endometriosis. The test diagnosed endometriosis with 95% sensitivity and 100% specificity."

Dr Bokor and the team of Prof D'Hooghe will do a blinded validation study in September 2009 to confirm the results of their research. "If this confirms our findings, we believe our research can be a solid base for a simple, reliable and relatively cheap method for non-invasive diagnosis of minimal and mild endometriosis, since trans-cervical endometrium sampling and immunohistochemical analysis are routine gynaecological and pathological procedures. Our research programme is also aimed at discovering new biomarkers that can enable a blood test for endometriosis to be developed," said Prof D'Hooghe.

More information:

[1] Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. *Human Reproduction* journal. doi:10.1093/humrep/dep275

[2] Density of small diameter sensory nerve fibres in endometrium: a

semi-invasive diagnostic test for mindoi:10.1093/humrepetriosis. *Human Reproduction* journal. doi:10.1093/humrep/dep283

[3] A pilot study to evaluate the relative efficacy of endometrial biopsy and full curettage in making a diagnosis of endometriosis by the detection of endometrial nerve fibers. Al-Jefout M, Andreadis N, Tokushige N, Markham R, Fraser I. *Am J Obstet Gynecol* 2007 Dec 197(6):578.e1-4

Source: European Society for Human Reproduction and Embryology (news : web)