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THE PRESIDENT's MESSAGE

"Singers come and go – but if you are a good actor you can last forever"*

Professor Hans Evers
WES President

We don't know why regurgitated endometrial fragments implant in one person and not in the other. What we do know is that implants will not last forever. Lesions come and go.

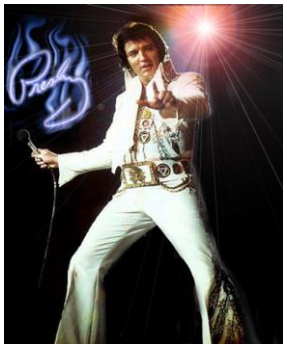
In the accumulated non-treated control groups of six randomized controlled trials, endometriosis was progressive in one third of patients, stable in another one third, whereas it had disappeared at the time of second look laparoscopy in the remaining one third.

This apparently is the result of an interaction between aggression (the menstrual debris) and defence (the peritoneal immune system). Either the reflux is too voluminous, or the immune system cannot cope, but in at least one third of patients the immune system prevails in the end. This should be kept in mind when judging the outcome of therapeutic trials in endometriosis.

Another thing that people often fail to notice is that the appearance of endometrial implants may change with ovarian activity. Performing a laparoscopy in a woman with active ovaries will show a dynamic, moist pelvis with productive, inflammatory, hyperaemic lesions producing mucus and blood.

During ovarian suppression on the other hand (e.g by danazol, by oral contraceptives, by progestogens, or by GnRH-a) the same lesions will be inactive, unproductive, or even invisible. There will be no inflammatory reaction surrounding them and the pelvis itself will be dry with muted hues.

Performing a second look laparoscopy during ovarian suppression is a mistake, it will provide a false sense of success, the lesions will still be there, although occult. Or, to quote The King again:



* Elvis Presley
(1935 – 1977)

"...truth is like the sun,
you can shut it out for a time,
but it ain't goin' away."

In this issue of the WES e-Journal

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A WORD FROM THE EDITOR

Dr Luk Rombauts
WES e-Journal Editor

This is the first anniversary of the e-Journal since taking over as editor from Professor Ali Akoum, and already the e-Journal changes its format! I will leave it up to you to decide whether this is an inability to stay the course or whether it a sign of embracing change.

We announced in the last issue that the main change in the format would be the inclusion of a section, named the Guest Editor's Digest. In this section the designated guest editor will select three abstracts of recently published papers that caught his/her eye. The abstracts will be included for quick reference. But more importantly, the guest editor will provide you with his/her take on the new developments/controversies for the sole purpose of making your continuous medical/scientific education more enjoyable.

We will continue to provide general news from our field, and reports from recent conferences, as well as the list of upcoming meetings so that you can keep your diaries filled.

We also continue to encourage debate, so don't hesitate to let us have your input and feedback to the news and opinions expressed in the e-Journal. The deadline for contributions to the next issue is 24 November 2009.

Finally: congratulations to Stephen Kennedy and Charles Koh with their recent awards!

UPCOMING MEETINGS

38th Annual Meeting of the AAGL
15 - 19 November 2009
Orlando, USA

Interaktiven Endometriose-Workshop
26 - 27 November 2009
Villach, Austria

II Internationaler Congress: Chinesische Medizin Endometriose, Reproduktionsmedizin, Mamma CA
18 - 20 February 2010
Weissensee, Austria

14th World Congress of Gynaecological Endocrinology
4 - 7 March, 2010
Firenze, Italy

Annual Scientific Meeting of the SGI
24 - 27 March 2010
Orlando, USA

ESHRE Campus: Endoscopy in reproductive medicine
25 - 27 November 2009
Leuven, Belgium

1st World Congress of the International Society for Fertility Preservation
10 - 12 December 2009
Brussels, Belgium

ESHRE Campus: Guideline for the Diagnosis and Treatment of Endometriosis
26 February 2010
Budapest, Hungary

Endometriosis 2010 - from bench to patient
18 - 20 March 2010
Milano, Italy

Ultrasound in deep endometriosis
24 April 2010
Rome, Italy

COMPLETE CONGRESS SCHEDULE

NEWS ROUND-UP

Stephen Kennedy is honoured with the Arnaldo Bruno Prize for Gynaecology


Stephen Kennedy
University of Oxford

Stephen Kennedy has been awarded this year's Arnaldo Bruno Prize for Gynaecology for his tremendous services to gynaecology, and to endometriosis in particular.

Mr Kennedy is the Clinical Reader in Obstetrics & Gynaecology and Head of the Nuffield Department of Obstetrics & Gynaecology at the University of Oxford in England. He is well-known for his work in endometriosis, in particular genetic epidemiology, health services research, the development of new diagnostic tests, and clinical drug trials. He jointly heads an international research group, which aims to identify the genes that predispose women to develop endometriosis.

Mr Kennedy is the author of a number of chapters and over 100 academic papers about endometriosis, and has edited a book entitled *Chronic Pelvic Pain*. He has prepared clinical guidelines for the Royal College of Obstetrics and Gynaecology (RCOG) on the management of both chronic pelvic pain and endometriosis, and he is a member of the working party that wrote the ESHRE Guideline for the Diagnosis Treatment of endometriosis. Kennedy is a founding board member of the World Endometriosis Research Foundation (WERF) and holds the position of secretary and treasurer.

The Arnaldo Bruno Prize was created in 2001 as the legacy of the late Amalia Bruno Frassetto in memory of the Italian gynaecologist, Arnaldo Bruno. The Prize is presented by the Accademia Nazionale dei Lincei in Rome - one of the oldest scientific academia in the world (alma mater to Galileo!).

Previous recipients include: Felice Petraglia (the first prize winner); Frederick Naftolin; John Challis; Dominique Henry Bellet; Linda Giudice; Basil Tarlatzis; and Marco Conti.

Many congratulations on a well-deserved recognition!

2009 SRS Distinguished Surgeon Award presented to Charles Koh


Dr Charles Koh receives the award presented by SRS president Keith Isaacson

Charles Koh was presented with the 2009 Distinguished Surgeon Award by the Society of Reproductive Surgeons (SRS) during the 65th Annual Meeting of the ASRM, in Atlanta on 20 October 2009, in recognition of his many contributions to the field of reproductive surgery.

Dr Koh graduated from the University of Singapore and trained in the University of London where he obtained his specialty degree in obstetrics and gynaecology.

He came to Milwaukee in 1977 as an assistant professor of obstetrics and gynaecology for the Medical College of Wisconsin and is currently the co-director of the Milwaukee Institute for Minimally Invasive Surgery and Reproductive Specialty Center.

Dr Keith Isaacson, President of the SRS, paid tribute to Dr Koh: "I am proud to present Dr Koh with the Distinguished Surgeon Award for 2009. In addition to the practice of infertility and in vitro fertilization, Dr Koh is a pioneer in advanced laparoscopic surgery for endometriosis and has lectured extensively on this internationally.

He also pioneered a special technique and equipment for laparoscopic hysterectomy called the 'Koh System for Total Laparoscopic Hysterectomy' and invented instruments for laparoscopic microsurgery. Dr Koh and his associate, Dr Grace Janik, were the first doctors in the world to perform laparoscopic microsurgical tubal anastomosis in 1992.

Dr Koh is most recently noted for his pioneering the first data proven curriculum for teaching laparoscopic suturing and

knot tying entitled 'Suturing in the Verticle Zone'. Using this technique he has instructed over 500 physicians. At the end of his one day course, approximately 90% of participants can accurately throw a suture and tie it intracorporeally in less than one minute."

Dr Koh recently completed a term as president of the Society of Laparoendoscopic Surgeons (SLS) and currently serves as a National Advisor for the American Association of Gynecologic Laparoscopists (AAGL).

Many congratulations on a well-deserved recognition!

WERF announces preliminary results from interim analysis of first two studies

A very well-attended session at the FIGO meeting in Cape Town in October 2009 was arranged by WES to address the epidemiology of endometriosis.

The session included three presentations with preliminary results from the interim analysis of the World Endometriosis Research Foundation's first two epidemiological studies: the Global Study of Women's Health (GSWH) and the Women's Health Symptoms Study (WHSS).

GSWH is addressing the global impact of endometriosis, whereas WHSS is looking at whether it is possible to predict the disease, with an ultimate goal of designing a symptom-based questionnaire to predict the presence of endometriosis. Both studies are prospective and involve 19 centres in 15 countries. Studies of this scale have never before been undertaken in the field of endometriosis.

The preliminary findings highlighted an average diagnostic delay of 8 years, with symptoms starting as young as 10 (two thirds of women reported symptoms before the age of 30!). The women had to see an average of six physicians before they were referred to their current physician.

It was significant that 26% of women with endometriosis had been referred to other specialists before their current gynaecologist compared with 14% of women without endometriosis. Approximately 50% of those "diagnosed" with irritable bowel syndrome (IBS) turned out to have endometriosis.

Women with endometriosis scored lower than symptomatic women who did not have endometriosis on all dimensions of general health as assessed by the 'SF36' (a questionnaire designed to assess general health and related functioning). This was explained by the fact that women with endometriosis experienced more severe pelvic pain than those without. Among employed women, endometriosis accounted for as much as 10 hours of work productivity lost per week.

Final results from the study, which is being coordinated by the University of Oxford, is expected to be submitted for publication in the first half of 2010.

Watch this space...

2010 charity calendar will be sold to support endometriosis research

Don't forget to purchase lots of 2010 calendars! – this beautiful calendar will raise money for the World Endometriosis Research Foundation's basic research fund! WERF hopes to raise sufficient funds in the next six months so that calls for proposals can be issued to researchers in this field ...and everyone can help make this happen, please!

The calendar makes a perfect Christmas present; and will look great on your office wall as well – so do consider buying plenty!

Please purchase calendars online at:
www.forourcause.org/thecalendar.html

Diagnostic laparoscopy for endometriosis: less is more

Luk Rombauts, MD, PhD, FRANZCOG, CREI

Clinical Senior Lecturer, MONASH University, Melbourne, Australia
Research Director, MONASH IVF, Melbourne, Australia, lrombauts@monashivf.edu.au

'Diagnostic laparoscopy for endometriosis: less is more' is the theme I selected for this first contribution in the Guest Editor's Digest series.

The first article I have selected (Daniels *et al*, 2009), was published only very recently in the Journal of the American Medical Association (JAMA). The JAMA has a stellar impact factor of 31.7 and for this reason alone it deserves pole position in this newly-styled contribution.

The principal aim of the LUNA trial collaboration was to conclude once and for all whether the ablation of the uterine nerve via laparoscopy is an effective means of treating women with chronic pelvic pain. The answer is it isn't.

At a first glance, the fact that the paper was published in JAMA may appear to be the only reason for its inclusion in the Digest. Indeed, subjects were not eligible for recruitment in this randomised controlled trial if they had anything more than very minimal endometriosis (excluded if rAFS score >5). Then why cast the spotlight on it in the WES e-Journal?

Firstly, it is a large randomised controlled trial. Let me rephrase this: it is a *very* large surgical RCT. Based on the sample size calculation the investigators needed to recruit a total of 175 women in each group (i.e. 350 in total) to detect a difference between groups of 1.2 cm on the VAS. They were fortunate enough to keep recruiting until a total of 487 patients were included, hereby minimizing the impact of loss-to-follow-up.

Secondly, that follow-up continued for up to five years. That is a very long time for any study. A total of 72% patients completed their five year follow-up, which is an outstanding result.

Thirdly, the investigators went to extreme lengths to minimize bias. Apart from the expected randomisation methods, the investigators also obtained ethics approval to perform sham incisions to make sure patients couldn't work out what group they had been allocated to.

Twelve months following surgery a subgroup of 211 patients were asked to guess what treatment arm they were randomised to and 58% guessed correctly. This is not significant and even if it was, it would only support the conclusion, because any degree of unblinding would have strengthened the treatment effect.

So what are the main conclusions?
This study confirms many other reports that most patients who present with chronic pelvic pain do not have endometriosis.

In actual fact, working out the numbers, only 35% (n=209) of the 592 patients assessed for inclusion had endometriosis.

The principle finding of the study, of course, is that LUNA does not improve any of the measures the authors looked at. Patients were asked to report on non-cyclical pain, dysmenorrhea, and dyspareunia. They also looked at a potential beneficial effect on health-related quality of life. Whether endometriosis was present or not did not alter the conclusion.

The current Cochrane review on this topic includes two studies with a combined total of 68 randomised patients. With 487 patients recruited the new study obviously represents a new milestone. It is hard to argue that the study is underpowered, but some may argue that the 1.2 cm VAS difference was chosen arbitrarily. The authors counteract this by referring to other studies where a clinically significant difference in pain has been defined as two points on a 10-point (cm) VAS for chronic pelvic pain. In addition, when looking only at the worst pain level experienced at 12 months, the pain score was only 0.02 cm lower in the LUNA group than in the no LUNA group.

My only surprise is that the authors seem to skirt around the observation that both interventions dropped the pain levels by about 2 cm on the VAS at 3 months.

So, although there is no difference *between* the interventions, *both* interventions appear to provide some level of pain relief following surgery. This could easily be brushed off as a temporary placebo effect, but interestingly, this effect does not appear to wane over time when looking at Figure 2 in the paper. Unfortunately, the authors do not provide statistics for these within-subject repeated observations, but I would be surprised if the sustained drop wasn't statistically significant.

Laparoscopic uterosacral nerve ablation for alleviating chronic pelvic pain: a randomized controlled trial
JAMA 2009;302(9):955-61.

Daniels J, Gray R, Hills RK, Latthe P, Buckley L, Gupta J, Selman T, Adey E, Xiong T, Champaneria R, Lilford R, Khan KS; LUNA Trial Collaboration.
Collaborators: Latthe P, Selman T, Daniels J, Adey E, Hills R, Hiller L, Buckley L, Xiong T, Champaneria R, Gair R, Powell R, Lynch L, Goodsell S, Hilken N, Tyler E, Wilcockson A, Khan KS, Latthe P, Selman T, Gupta JK, Mann C, Clark TJ, Newton J, Chien P, Macleod M, Thornton J, Rose E, Connor M, Baxter A, Farrell T, Bonner C, Kay V, Crystal W, Pheely M, Irani S, Dwarakanath L, Hollingworth J, Honest H, Chin K, Kabukoba J, Samra JS, Cox CW, Fender GR, Ismail KM, Keay S, Awadzi G, Shaxted EJ, Hitchcock R, Smith J, Zakaria M, Beecham N, Phillips WD, Brocklehurst P, Jordan J, Braunholtz P, Sandercock J.

CONTEXT: Chronic pelvic pain is a common condition with a major effect on health-related quality of life, work productivity, and health care use. Operative interruption of nerve trunks in the uterosacral ligaments by laparoscopic uterosacral nerve ablation (LUNA) is a treatment option for patients with chronic pelvic pain.
OBJECTIVE: To assess the effectiveness of LUNA in patients with chronic pelvic pain.
DESIGN, SETTING, AND PARTICIPANTS: Randomized controlled trial of 487 women with chronic pelvic pain lasting longer than 6 months without or with minimal endometriosis, adhesions, or pelvic inflammatory disease, who were recruited to the study by consultant gynecological surgeons from 18 UK hospitals between February 1998 and December 2005. Follow-up was conducted by questionnaires mailed at 3 and 6 months and at 1, 2, 3, and 5 years.
INTERVENTION: Bilateral LUNA or laparoscopy without pelvic denervation (no LUNA); participants were blinded to the treatment allocation. MAIN OUTCOME MEASURES: The primary outcome was pain, which was assessed by a visual analogue scale. Data concerning the 3 types of pain (noncyclical pain, dysmenorrhea, and dyspareunia) were analyzed separately as was the worst pain level experienced from any of these 3 types of pain. The secondary outcome was health-related quality of life, which was measured using a generic instrument (EuroQoL EQ-5D and EQ-VAS).
RESULTS: After a median follow-up of 69 months, there were no significant differences reported on the visual analogue pain scales for the worst pain (mean difference between the LUNA group and the no LUNA group, -0.04 cm [95% confidence interval {CI}, -0.33 to 0.25 cm]; P = .80), noncyclical pain (-0.11 cm [95% CI, -0.50 to 0.29 cm]; P = .60), dysmenorrhea (-0.09 cm [95% CI, -0.49 to 0.30 cm]; P = .60), or dyspareunia (0.18 cm [95% CI, -0.22 to 0.62 cm]; P = .40). No differences were observed between the LUNA group and the no LUNA group for quality of life.
CONCLUSION: Among women with chronic pelvic pain, LUNA did not result in improvements in pain, dysmenorrhea, dyspareunia, or quality of life compared with laparoscopy without pelvic denervation. TRIAL REGISTRATION: controlled-trials.com Identifier: ISRCTN41196151.

Now, how does this paper relate to the 'theme'?
Well, the study illustrates once more the low likelihood of finding endometriosis in patients with chronic pelvic pain.

Similar observations apply to patients with infertility. So the question arises whether we can find better ways of pre-operatively selecting those patients that may actually benefit from surgery. That is where the next three selected articles fit in. Those articles discuss two novel methodologies that may perhaps lead to less invasive screening tests.

The next two papers I will discuss together, because they were published in the same issue of Human Reproduction and investigate the same topic. The research groups of Professor Ian Fraser and Professor Thomas D'Hooghe both independently report on the use of immunohistochemical markers used to stain nerve fibres in the endometrium.

Professor Fraser's group had previously caused some commotion at the WCE 2008 meeting in Melbourne by claiming an almost 100% accuracy of the test. In the September 2008 issue of the WES e-Journal our President warned: "Another striking thing at this meeting were the many biomarker studies, indicating differences between women with endometriosis and women without endometriosis, claiming that a new diagnostic test would soon become available with sensitivities and specificities of up to 100%. These conclusions never stand firm after proper clinical evaluation in an independent second group of patients. In our field of specialty sensitivities and specificities of 75% are not bad at all, so something may come out of these studies eventually, but so far the claims seem to be a little exaggerated." True to his reputation as a thorough investigator, Ian Fraser has now provided us with further data, which we can immediately test for external validity by comparing his findings with those from the Leuven group.

Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study
Hum Reprod 2009 Aug 18 [Epub ahead of print]

Al-Jefout M, Dezarnaulds G, Cooper M, Tokushige N, Luscombe GM, Markham R, Fraser IS.

BACKGROUND Diagnosis of endometriosis currently requires a laparoscopy and this need probably contributes to the considerable average delay in diagnosis. We have reported the presence of nerve fibres in the functional layer of endometrium in women with endometriosis, which could be used as a diagnostic test. Our aim was to assess efficacy of nerve fibre detection in endometrial biopsy for making a diagnosis of endometriosis in a double-blind comparison with expert diagnostic laparoscopy.
METHODS Endometrial biopsies, with immunohistochemical nerve fibre detection using protein gene product 9.5 as marker, taken from 99 consecutive women presenting with pelvic pain and/or infertility undergoing diagnostic laparoscopy by experienced gynaecologic laparoscopists, were compared with surgical diagnosis.
RESULTS In women with laparoscopic diagnosis of endometriosis (n = 64) the mean nerve fibre density in the functional layer of the endometrial biopsy was 2.7 nerve fibres per mm(2) (+/-3.5 SD). Only one woman with endometriosis had no detectable nerve fibres. Six women had endometrial nerve fibres but no active endometriosis seen at laparoscopy. The specificity and sensitivity were 83 and 98%, respectively, positive predictive value was 91% and negative predictive value was 96%. Nerve fibre density did not differ between different menstrual cycle phases. Women with endometriosis and pain symptoms had significantly higher nerve fibre density in comparison with women with infertility but no pain (2.3 and 0.8 nerve fibre per mm(2), respectively, P =0.005).
CONCLUSIONS Endometrial biopsy, with detection of nerve fibres, provided a reliability of diagnosis of endometriosis which is close to the accuracy of laparoscopic assessment by experienced gynaecological laparoscopists. This study was registered with the Australian Clinical Trials Registry (ACTR) 00082242 (registered: 12/12/2007). The study was approved by the Ethics Review Committee (RPAH Zone) of the Sydney South West Area Health Service (Protocol number X05-0345) and The University of Sydney Human Research Ethics Committee (Ref. No. 10761) and all women gave their informed consent for participation.

Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis
Hum Reprod 2009 Aug 18 [Epub ahead of print]

Bokor A, Kyama CM, Vercruysse L, Fassbender A, Gevaert O, Vodolazkaia A, De Moor B, Fülöp V, D'Hooghe T.

BACKGROUND The aim of our study was to test the hypothesis that multiple-sensory small-diameter nerve fibres are present in a higher density in endometrium from patients with endometriosis when compared with women with a normal pelvis, enabling the development of a semi-invasive diagnostic test for minimal-mild endometriosis.
METHODS Secretory phase endometrium samples (n = 40), obtained from women with laparoscopically/histologically confirmed minimal-mild endometriosis (n = 20) and from women with a normal pelvis (n = 20) were selected from the biobank at the Leuven University Fertility Centre. Immunohistochemistry was performed to localize neural markers for sensory C, Adelta, adrenergic and cholinergic nerve fibres in the functional layer of the endometrium. Sections were immunostained with anti-human protein gene product 9.5 (PGP9.5), anti-neurofilament protein, anti-substance P (SP), anti-vasoactive intestinal peptide (VIP), anti-neuropeptide Y and anti-calcitonine gene-related polypeptide. Statistical analysis was done using the Mann-Whitney U-test, receiver operator characteristic analysis, stepwise logistic regression and least-squares support vector machines.
RESULTS The density of small nerve fibres was approximately 14 times higher in endometrium from patients with minimal-mild endometriosis (1.96 +/- 2.73) when compared with women with a normal pelvis (0.14 +/- 0.46, P < 0.0001).
CONCLUSIONS The combined analysis of neural markers PGP9.5, VIP and SP could predict the presence of minimal-mild endometriosis with 95% sensitivity, 100% specificity and 97.5% accuracy. To confirm our findings, prospective studies are required.

The good news is that both studies, although still small, seem to allay the well-founded concerns of our President. The reported sensitivities are 98% and 95% and the specificities are 83% and 100%, respectively. If we argued that larger confirmatory studies might 'settle' the sensitivity at 95% and the specificity at 85%, then this type of test would miss one patient with endometriosis out of twenty with the disease and it would incorrectly refer one out of seven women without the disease for a laparoscopy. Those odds aren't bad at all; certainly a significant improvement on current practice.

The study by Al-Jefout *et al* also seems to have refuted their own initial findings that the nerve density varies with the cycle, which would make it a lot easier to schedule the test. In addition, the severity of the disease didn't seem to affect the readings either. The study by Bokor *et al* takes a somewhat different approach by investigating which combination of nerve fibre markers delivers the best test.

So, what are the remaining issues?
Although very encouraging, the studies are still too small to be conclusive. Taken together, both studies examined less than 140 patients. There is also the issue of referral bias, particularly in the first study where endometriosis was present in 63% of the patients. The utility of a diagnostic test depends on the prevalence in the screening population, and the value of these tests therefore needs to be investigated in larger and less selected populations.
Another issue is that the test won't work if the patient has been taking hormonal treatment. That is a little bit of a blow given that the oral contraceptive pill tends to be first-line treatment of choice for endometriosis.

It also remains to be seen how soon after discontinuing the pill the test can be offered, that is assuming that patients will accept to come off the medication. Both groups also point to the importance of the technical aspects, such as the sampling technique, the immunohistochemical staining, and perhaps even the statistical models to predict the risk. This can sound like nit-picking, but diagnostic tests always perform better under laboratory conditions than in real-life.

Finally, an endometrial biopsy is, and I quote from the paper by Bokor *et al*, "an acceptable semi-invasive technique, much less invasive than a laparoscopy, but still possibly associated with some degree of pelvic pain at the time of biopsy." So, where are we with those serological tests that we were promised such a long time ago? There too the future remains uncertain, despite it being the focus of much research activity. Nevertheless, there are a few developments that are worth following. One of them is the field of microRNAs. The group of Louise Hull has reviewed the literature to which they have significantly contributed and it makes for a good read for those of us that are more molecularly inclined. For those interested, I would also recommend a recent paper by Linda Giudice's group (Mol Hum Reprod 2009 Oct;15(10):625-31).

There is enough evidence now to show that the microRNA profiles are different in the eutopic endometrium from women with and without the disease and it also appears dysregulated in the endometriotic lesions themselves. There are indications from studies in the cancer field that the disease-specific microRNA profiles in the tissue 'leak' into the circulation. This obviously opens up the prospect of a serological test for endometriosis. So, watch this space…

The role of microRNAs in endometriosis and associated reproductive conditions
Hum Reprod Update 2009 Sep 22 [Epub ahead of print]

Ohlsson Teague EM, Print CG, Hull ML.

BACKGROUND microRNAs (miRNAs) are short, single-stranded RNAs that regulate gene expression at the post-transcriptional level. Recent research has shown that miRNAs and their target mRNAs are differentially expressed in endometriosis and other disorders of the female reproductive system. Since miRNAs control a broad spectrum of normal and pathological cellular functions, they may play pivotal roles in the pathogenesis of these disorders.
METHODS A systematic review was undertaken of the published literature on; (i) the expression and functions of miRNAs in mammalian female reproductive tissues with a focus on endometriosis and the malignancies and fertility disorders related to this disease; and (ii) the potential roles played by validated mRNA targets of endometriosis-associated miRNAs. The current understanding of the biology of miRNAs is overviewed and the potential diagnostic and therapeutic potential of miRNAs in endometriosis is highlighted.
RESULTS The differential expression of miRNAs in endometriosis, and the putative molecular pathways constituted by their targets, suggests that miRNAs may play an important role in endometriotic lesion development. Models for miRNA regulatory functions in endometriosis are presented, including those associated with hypoxia, inflammation, tissue repair, TGFbeta-regulated pathways, cell growth, cell proliferation, apoptosis, extracellular matrix remodelling and angiogenesis. In addition, specific miRNAs which may be associated with malignant progression and subfertility in endometriosis are discussed.
CONCLUSIONS miRNAs appear to be potent regulators of gene expression in endometriosis and its associated reproductive disorders, raising the prospect of using miRNAs as biomarkers and therapeutic tools in endometriosis.