

THE PRESIDENT'S MESSAGE

At the movies

Yvonne: "Where were you last night?"
 Rick: "That's so long ago, I don't remember."
 Yvonne: "Will I see you tonight?"
 Rick: "I never make plans that far ahead."

This crisp dialogue, from the movie Casablanca, with Humphrey Bogart, the son of a New York surgeon, in the role of Rick, has always intrigued me. Oh, to be in the movies and deliver a snappy text like this...

And now we are in the movies!

On 11 March 2011, the World Endometriosis Society launched its much longed-for endometriosis awareness film. With Diana Wallis, the European Parliament vice-president, in a leading role: "Don't be like me. Don't take no for an answer. If you feel something is wrong, you could have endometriosis. There are things that can be done to help you. Go and get advice, but also make others aware, because I don't want you to end up like me", said Diana.

Diana Wallis is a long time sufferer herself. She resists the dismissive attitude towards her symptoms: "Over a period of 10 years, I was told 'you're working too hard as a professional woman – take it easy'". She had a hysterectomy as a newlywed, an operation that maybe could have been avoided with earlier diagnosis and treatment of her endometriosis. She was never able to have children. Today, she urges young women not to compromise their fertility, like she did, and get help, and treatment, early.

If you have not seen the movie yet, please visit <http://vimeo.com/20910143> and, even better, share it with your patients and their (and your) daughters.

Women themselves know best what is too much pain. There is a difference between menstrual discomfort, and pain that prevents you from going about your daily life. WES has created this film to help educate women about what is *not* normal when it comes to pain. It highlights the symptoms of endometriosis, explains the way to diagnose it and discusses treatment options, both in case of infertility as well as pain. The film is targeting adolescents and young women. It encourages those who recognize these symptoms to seek help before their health is affected irreversibly.

So, next year you better watch the 84th Academy Awards ceremony at Hollywood's Kodak Theatre. Many millions of viewers worldwide will tune in to the thrill and allure of Oscar Night, and you can delight in the excitement while Diana Wallis, Lone Hummelshoj and me will stride down the red carpet, together with Nicole Kidman and Clint Eastwood, cheered by the fans. Or will we?

Maybe better to quote Bogie one more time: "A hotdog at the ballpark is better than a steak at the Ritz". This is a mighty fine little film indeed!



Professor Hans Evers
WES President

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ISSN 1993-3924

A WORD FROM THE EDITOR

Counting down...

It is less than 100 days now before the opening of the World Congress of Endometriosis in Montpellier. The suspense is increasing, the excitement is growing. Travel plans are taking shape with pre- and post-conference tours in the South of France booked into the diary. Worldwide, administrators in hospital and university departments receive a constant stream of leave forms and are scratching their head over the gaps to fill in their O&G on-call rosters.

At the same time, the excitement at the World Endometriosis Society headquarters is building too. The deadline for abstract submission closed on the 31st of March. A total of 517 abstracts were sent in and the abstract committee went through the difficult task of selecting which abstracts were accepted in which category. The abstract selection process is based on a blinded, international, peer review process to ensure all abstracts are reviewed by several experts in our field. The five best abstracts for each seminar topic will be introduced by a world-renowned expert and then given centre stage with ample time to present the work in detail—and to discuss it with the audience.

A further 52 accepted abstracts will be presented in ten oral communications sessions, and 350 posters distributed over three breakfast poster sessions will be displayed. The prestigious Rudolphe Maheux Award, which carries a cash prize of €1,000, will be presented at the closing ceremony to the first author and presenter of the best clinical oral presentation or poster. The award aims to stimulate clinical research by young investigators under the age of 40 years. Four travel grants have also been awarded to meritorious registrants who were unable to find financing to come and present their work.

I am sad to announce that our President, Hans Evers, may soon be leaving us for a career in the film industry. I don't want to start any rumours, but in this issue of the WES eJournal, he suggests that he thoroughly enjoyed his acting role in the recently launched film on endometriosis. I am wondering, will he still remember us when he gets his star on Hollywood's Walk of Fame? On a more serious note, I was very impressed with the presentation and content of the film and will certainly be directing my patients to this valuable resource.

Finally, in this issue, it is Professor Linda Guidice's turn to offer us a Guest Editor's Digest. She has reviewed the four most interesting endometriosis papers and explains her reasons for selecting them for our members.

Happy Reading!



Dr Luk Rombauts
WES e-Journal Editor

UPCOMING MEETINGS

27th Annual Meeting of ESHRE

3 - 6 July 2011
Stockholm, Sweden

11th World Congress on Endometriosis (WCE2011)

4 - 7 September 2011
Montpellier, France

20th Annual Congress of the ESGE

21 - 24 September 2011
London, England

67th Annual Meeting of the ASRM

15 - 19 October 2011
Orlando, USA

>> **COMPLETE CONGRESS SCHEDULE**

The impact of the reproductive tract environment on implantation success

3 July 2011
Stockholm, Sweden

20th SLS Annual Meeting and Endo Expo

14 - 17 September 2011
Los Angeles, USA

Endometriosis: the link between pathophysiology and treatment

16 October 2011
Orlando, USA

ESHRE Campus: Endometriosis and IVF

28 - 29 October 2011
Rome, Italy

Hot topics in basic research in endometriosis

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Professor Linda Giudice

Epigenetics, small RNAs, and stem cells are broadening the horizon of understanding the pathogenesis and pathophysiology of endometriosis. For this Research Digest, I have chosen four recently published articles focusing on these rapidly changing areas of science applied to endometriosis.

Epigenetics

Epigenetics involves modifications of chromatin that affect regulation of gene expression but do not alter DNA sequence. Methylation of the carbon-5 position of cytosines in CpG dinucleotides is the main epigenetic modification of DNA. This article demonstrates steroid hormone dependence in eutopic endometrium and endometriotic implants of genes regulating DNA methylation (DNA methyl transferases) and function (methyl CpG binding proteins (MeCpGBPs)).

There is increasing evidence of epigenetic regulation of steroid hormone action in various tissues, including endometrium and abnormalities in women with endometriosis. Genome-wide profiling of methylated promoters in endometriosis lesion sub-types and endometrium revealed hyper-

and hypo-methylation unique to these groups, and altered methylation status of promoters for transcription factors (e.g., HoxA10, steroidogenic factor-1, ERbeta) contribute to the phenotype of progesterone resistance in endometriosis. This area of research is likely to be mined extensively over the next 2-5 years, giving major insights into the pathogenesis/ physiology of endometriosis.

Small RNAs

Several RNA species have been identified that regulate gene expression and biological processes, including microRNAs, which are non-coding RNAs that usually inhibit their messenger RNAs targets.

The article on the next page found higher levels of miRNAs whose mRNA targets are related to angiogenesis in peritoneal lesions and lower levels in ovarian endometriomas, compared to eutopic endometrium.

Deoxyribonucleic acid methyltransferases and methyl-CpG-binding domain proteins in human endometrium and endometriosis

Fertil Steril 2011; Feb 12 (Epub ahead of print)

van Kaam KJ, Delvoux B, Romano A, D'Hooghe T, Dunselman GA, Groothuis PG

OBJECTIVE: To determine [1] expression levels of both DNA methyltransferases (DNMTs) and methyl-CpG-binding domain proteins (MBDs) in human endometrium throughout the menstrual cycle and in eutopic and ectopic endometrium of patients with endometriosis and [2] hormone responsiveness of DNMT and MBD expression in explant cultures of proliferative phase endometrium. **DESIGN:** In vitro study. **SETTING:** Academic medical center. **PATIENT(S):** Premenopausal women with and without endometriosis. **INTERVENTION(S):** Explant cultures of proliferative phase endometrium were treated with vehicle, 17 β -E(2), or a combination of E(2) and P (E(2) + P) for 24 hours. **MAIN OUTCOME MEASURE(S):** Expression levels of DNMT1, DNMT2, and DNMT3B and MBD1, MBD2, and MeCP2 with use of real-time quantitative polymerase chain reaction. **RESULT(S):** Expression levels of DNMT1 and MBD2 were significantly higher in secretory-phase endometrium compared with proliferative endometrium and menstrual endometrium. In explant cultures, treatment with E(2) + P resulted in significant up-regulation of DNMT1 and MBD2. Expression levels of several DNMTs and MBDs were significantly lower in endometriotic lesions compared with eutopic endometrium of women with endometriosis and disease-free controls. **CONCLUSION(S):** These findings suggest a role for DNMTs and MBDs in the growth and differentiation of the human endometrium and support the notion that endometriosis may be an epigenetic disease.

microRNA expression in endometriosis and their relation to angiogenic factors

Hum Reprod 2011;26(5):1082-90.

Ramón LA, Braza-Boïls A, Gilabert-Estellés J, Gilabert J, España F, Chirivella M, Estellés A.

BACKGROUND Endometriosis is a common, multifactorial disease in which angiogenesis may be involved in the growth of endometrium outside the uterus. microRNAs (miRNAs) are 21-22 nucleotide non-coding RNAs that regulate gene expression and play fundamental roles in biological processes. The objective of this study was to analyze several miRNAs related to angiogenesis and the angiogenic factors, vascular endothelial growth factor-A (VEGF-A) and thrombospondin-1 (TSP-1), in endometriotic lesions (ovarian endometrioma, peritoneal lesion and rectovaginal nodule) and eutopic endometrium from women with endometriosis. **METHODS** TaqMan real-time PCR was used to assess the expression of the miRNAs (miR-15b, -16, -17-5p, -20a, -21, -125a, -221 and -222), while VEGF-A and TSP-1 mRNA were assessed by real-time PCR, with SYBR Green I and VEGF-A and TSP-1 protein levels were quantified by ELISA. Included in the study were 58 women with endometriosis and 38 control women. **RESULTS** In paired samples, ovarian endometrioma showed significantly lower VEGF-A mRNA ($P=0.02$) and protein ($P=0.002$) expression than eutopic endometrium and higher expression of miR-125a ($P=0.003$) and miR-222 ($P<0.001$). However, ovarian endometrioma had significantly higher expression of the angiogenic inhibitor TSP-1 and lower expression of miR-17-5p than eutopic endometrium ($P<0.001$). Moreover, a significant inverse correlations between miR-222 and VEGF-A protein levels (-0.267 , $P=0.018$) and between miR-17-5p and TSP-1 protein levels (-0.260 , $P=0.022$) were observed. Peritoneal lesions showed a significant increase in VEGF-A in comparison with ovarian endometrioma ($P<0.01$). **CONCLUSIONS** Ex-

These differences may affect expression of angiogenic factors important in the pathogenesis and pathophysiology of endometriosis.

This next study performed the first transcriptome-microRNAome analysis of endometriomas and eutopic endometrium using next-generation sequencing technology. A total of more than 54 million independent small RNA reads from 19 clinical samples were generated.

Some miRNAs were up-regulated and some were down-regulated. That such differences had functional relevance was tested in endometrial stromal fibroblasts in vitro, in which extracellular matrix targets of miR-29c, e.g., were downregulated when miR-29c was overexpressed.

This approach underscores the contribution of microRNAs in the pathophysiology of endometriosis.

Functional MicroRNA involved in endometriosis

Mol Endocrinol 2011;25(5):821-32.

Hawkins SM, Creighton CJ, Han DY, Zariff A, Anderson ML, Gunaratne PH, Matzuk MM.

Endometriosis is a common disease seen by gynecologists. Clinical features involve pelvic pain and unexplained infertility. Although endometriosis is pathologically characterized by endometrial tissue outside the normal uterine location, endometriosis is otherwise not easily explained. Endometriomas, endometriotic cysts of the ovary, typically cause pain and distortion of pelvic anatomy. To begin to understand the pathogenesis of endometriomas, we describe the first transcriptome-microRNAome analysis of endometriomas and eutopic endometrium using next-generation sequencing technology. Using this approach, we generated a total of more than 54 million independent small RNA reads from our 19 clinical samples. At the microRNA level, we found 10 microRNA that were up-regulated (miR-202, 193a-3p, 29c, 708, 509-3-5p, 574-3p, 193a-5p, 485-3p, 100, and 720) and 12 microRNA that were down-regulated (miR-504, 141, 429, 203, 10a, 200b, 873, 200c, 200a, 449b, 375, and 34c-5p) in endometriomas compared with endometrium. Using in silico prediction algorithms, we correlated these microRNA with their corresponding differentially expressed mRNA targets. To validate the functional roles of microRNA, we manipulated levels of miR-29c in an in vitro system of primary cultures of human endometrial stromal fibroblasts. Extracellular matrix genes that were potential targets of miR-29c in silico were significantly down-regulated using this biological in vitro system. In vitro functional studies using luciferase reporter constructs further confirmed that miR-29c directly affects specific extracellular matrix genes that are dysregulated in endometriomas. Thus, miR-29c and other abnormally regulated microRNA appear to play important roles in the pathophysiology of uterine function and dysfunction.

Stem Cells

This recent article reviews endometrial stem cells and their potential roles in regeneration of cycling endometrium as well as in the pathogenesis of endometriosis and extra-pelvic endometriosis.

In addition, the multi-potency of endometrial stem/progenitors underscores their potential uses in regenerative medicine.

Stem cells in endometrium and their role in the pathogenesis of endometriosis

Ann N Y Acad Sci 2011;1221:10-7.

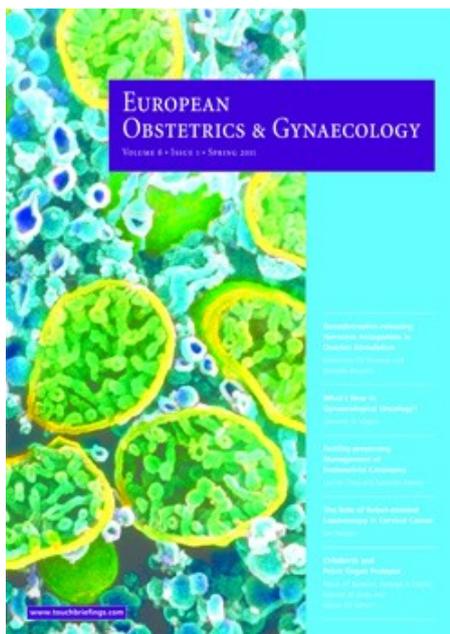
Figueira PG, Abrão MS, Krikun G, Taylor H.

The human **endometrium** is a dynamic tissue that undergoes cycles of growth and regression with each menstrual cycle. Adult progenitor/stem cells are likely responsible for this remarkable regenerative capacity; these same progenitor stem cells may also have an enhanced capacity to generate endometriosis if shed in a retrograde fashion. The progenitor stem cells reside in the uterus; however, less-committed mesenchymal stem cells may also travel from other tissues such as bone marrow to repopulate the progenitor population. Mesenchymal stem cells are also involved in the pathogenesis of endometriosis and may be the principle source of endometriosis outside of the peritoneal cavity when they differentiate into endometriosis in ectopic locations. Finally, besides progenitor stem cells, recent publications have identified multipotent stem cells in the endometrium. These multipotent stem cells are a readily available source of cells that are useful in tissue engineering and regenerative medicine. Endometrial stem cells have been used to generate chondrocytes, myocytes, neurons, and adipocytes in vitro as well as to replace dopaminergic neurons in a murine model of Parkinson's disease.

NEWS and ANNOUNCEMENTS

European *Obstetrics and Gynaecology* available free to all WES members

As part of our collaboration with Touch Briefings, WES members receive free eBook access to their **European Obstetrics & Gynaecology** journal (members also get access to the **US Obstetrics and Gynecology** journal, see: <http://www.endometriosis.ca/publications.html>)



In this latest issue, Udo D Hoyme contributes an excellent article on the prevention of pre-term birth with vaginal self-screening, while Giovanni Di Vagno asks: “What’s new in gynaecological oncology?”

Elsewhere in this issue, Jan Persson takes a look at the role of robot-assisted laparoscopy in cervical cancer.

Directed by an editorial board comprising internationally respected physicians, *European Obstetrics & Gynaecology*'s peer-reviewed articles endeavour to provide a concise and timely update on the latest opinion and advances spanning the breadth of obstetric and gynaecological practice.

WES members can access the current edition, of *European Obstetrics & Gynaecology* (Volume 6 Issue 1) in full and for free by clicking through to www.touchobgyn.com/journals/editions/european-obstetrics-gynaecology-volume-6-issue-1

If you wish to receive a hard copy of the journal, please send an email to: miriam.oppenheim@touchbriefings.com

WES presidential initiatives focus on providing factual information

WES was founded in 1997 at the 6th World Congress on Endometriosis (Quebec, Canada).

Those who decided to commit themselves to starting this society were passionate about moving the field of endometriosis forward—which is why they dedicated their time to start, evolve, and manage this society.

This ethic has not changed with any future board composition: it is about getting better at understanding endometriosis and making that knowledge freely available!

And, there has been a common thread...

The first president of WES, Professor Jacques Donnez, wanted to fill a void by providing widely available information about the disease. He developed a CD ROM about endometriosis at a time when the Internet was in its infancy ...and CD ROMs were cutting edge!

Moving with the times

WES's 4th president, Professor Rodolphe Maheux, didn't stray from this vision of getting information out there—and involving everyone who wanted to contribute to our field; regardless of geography.

Regretfully Professor Maheux died before he could implement his vision. Thankfully the WES board set out to do so on his behalf — and to honour him in this process — by instigating two awards:

- The Rodolphe Maheux Award for a young, promising clinician in the field of endometriosis (awarded to the best abstract presentation at each WCE).

- The Rodolphe Maheux Travel Grant for young, promising researchers enabling them to attend WCEs (awarded to young researchers who cannot obtain financing to attend WCEs where their abstract(s) have been accepted). The ability to provide these grants has been made possible through generous donations by WES members.

From CD ROM to the Internet

Our current president, Hans Evers, has not strayed from this mission of ensuring awareness and readily available information.

Last year WES published, together with WERF, a much needed FACT sheet about the disease. It made it clear what endometriosis is—and what we know about the disease right now. Nothing more — nothing less. In one page:

<http://www.endometriosis.ca/facts-about-endometriosis.pdf>

But, most importantly: WES has now produced the first ever online film about:

- what endometriosis is
- theories about the causes of the disease
- how it is currently diagnosed and treated
- what resources are available to support sufferers

With almost 11,000 plays so far this is a tremendous achievement and success for WES for its long standing quest to raise factual awareness of endometriosis!

We urge you all to spread the word, share the film, and let us know if you want this to be available in your language as well! [Do share the film with everyone!](#) Please!



43 countries will be presenting data on endometriosis at WCE2011

The record for abstract submission to any WCE has been broken! In fact we have seen an all time surge in the interest in endometriosis never surpassed before: 517 abstracts have been submitted to WCE2011!!

WES is delighted and the WES Board of Trustees have only one comment: “It shows the world how important endometriosis is!! — and let’s encourage everyone who is serious about endometriosis to register for WCE2011 and to be part of the largest World Congress on Endometriosis!“. Register online at <http://www.wce2011.com>.

Abstracts accepted for presentation at WCE2011 by country:

