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THE PRESIDENT's MESSAGE

Crystal balls

Professor Hans Evers
WES President

Prognostic modelling is 'hot'.

In reproductive medicine, various prognostic models (and even meta-prognostic models!) have been developed to predict the treatment-dependent and treatment-independent occurrence of a pregnancy in subfertility couples.

In our field of clinical interest, John Sampson, Anibal Acosta and Veasy Buttram were amongst the many who developed predecessors to the "AFS classification" and "rAFS classification" for endometriosis, now widely used around the world; not only to document the stage of endometriosis but also to predict the occurrence of pregnancy. And estimating individual pregnancy chances was not what this classification was meant to do. And thus people got frustrated, which is illustrated by the fact that (in order to obtain some differentiation of outcomes) in the majority of clinical studies using these classifications, the stages "minimal" and "mild" are lumped together, as are "moderate" and "severe".

The cartoonist Scott Adams once had his character Dilbert explain that there are many ways for predicting the future. For example you can read horoscopes, tea leaves, tarot cards, or crystal balls. Collectively, these methods are known as "nutty methods." Or you can put well-researched facts into sophisticated computer models, more commonly referred to as "a complete waste of time" (S. Adams, 2000: *The Dilbert Future*).

Why did so many classification systems fail to predict the future? Because most of them were never validated in an independent second sample of patients. Predicting outcome may be very promising in the group in which the model was developed. However, it may turn out to be a complete failure in a group of the same patients at another time, in another part of the world.

And now we have the EFI, the Endometriosis Fertility Index, developed by David Adamson and David Pasta, a "simple, robust, and validated clinical tool that predicts pregnancy rates after surgical staging" (Fertil Steril 2009, Nov 18 Epub ahead of print), the first tool we can use in our clinics to document the severity and extent of endometriosis *and* estimate the spontaneous pregnancy chances. Couples with a good prognosis can be reassured and, according to their personal preferences, convinced to wait for a spontaneous pregnancy to occur; poor prognosis couples can be referred for treatment immediately.

It will be interesting to learn how this robust tool will perform in other groups of endometriosis patients. Something for a world-wide, multicenter, multi-national WES initiative?

In this issue of the WES e-Journal

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A WORD FROM THE EDITOR

Dr Luk Rombauts
WES e-Journal Editor

In this last issue before the festive season starts, we have a new Guest Editor's Digest, this time by Professor Liselotte Mettler. She has selected five recent articles from the literature.

From her comments it is fair to say that she is a strong advocate for early surgical intervention, preferably in dedicated units. She also uses the association between ovarian endometriomata and ovarian cancer to argue in favour of surgical treatment for endometriomata.

This is perhaps worth exploring a little further, especially given the recent debate regarding the pros and cons of endometrioma removal in the context of infertility treatment.

It has long been known that women with certain epithelial ovarian cancers have a higher prevalence of endometriosis.

Indeed, the prevalence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5%, 1.4%, 35.9%, and 19.0% for serous, mucinous, clear-cell and endometrioid ovarian carcinoma, respectively (Van Gorp T et al, 2004).

Fortunately, ovarian cancer is relatively uncommon compared to breast cancer. So, how common then is endometriosis-related ovarian cancer? There are a number of approaches to look at this.

There are two large studies I would like to highlight. The first one is a case-control study by Brinton et al (1997). This study included 20,686 women with a hospital discharge diagnosis of endometriosis during a mean 11.4-year follow-up period, the records of which were linked to the Swedish Cancer Registry. Compared to women who had never been diagnosed with endometriosis, their relative risk (RR) for developing a malignancy of the ovary was significantly increased to 1.92 (95% CI 1.3–2.8). The RR was increased to 4.20 (95% CI 2.0–7.7) when the endometriosis was confined to the ovary.

To work out roughly how many women this represents, we need to do a few 'back of an envelope' calculations.

- The incidence rate (new cases per year) of ovarian cancer is about 1 per 10000 women (or 100/1,000,000 women).
- These 100 new ovarian cancers per year arise in a population of 1,000,000 women with and without endometriosis.
- Let's assume that the population prevalence of endometriosis is 10%. This means that 100,000 of these 1,000,000 women will have endometriosis.
- If we accept Brinton's findings that the RR in women with endometriosis is approximately 2-fold increased, then 18 of the 100 ovarian malignancies will have arisen in women with endometriosis.
- 18/100,000 is twice as high as 82/900,000. Given that the RR is approximately 2, half of those eighteen malignancies would have arisen anyway, the other nine because of the association with endometriosis; this equates to an excess risk of about 1 ovarian cancer in every 10,000 women with endometriosis.

When contemplating this excess risk of 1/10,000 it is important to remember that, when Brinton stratified the risk for length of follow-up, a statistically significant increase in the RR was only observed in the subgroup of women with >10 years follow-up (RR 2.51; 95% CI 1.4–4.1).

In other words, endometriosis-related cancers were far more common in older women. Eržen et al. (1998) also noted the age-related distribution of endometriosis-related ovarian malignancies: ≤19 years, 0%; 20–29 years, 1.9%; 30–39 years, 1.0%; 40–49 years, 2.4%; 50–59 years, 12%, 60–69 years, 58%; ≥70 years, 80%. So, the risk of 1/10,000 is a lot lower again in the age group where we may consider to delay excision until after fertility treatment.

The other study is a recent study by Kobayashi et al. (2008), prospective and longitudinal in design. The study estimates the standardized incidence ratio (SIR: ratio of the observed number of cancer cases to the expected number of cases) to be almost 9 (95% CI: 4.1–15.3). Although this estimate is clearly concerning, the vast majority of these cancers originated in menopausal women with endometriomata >9cm in diameter.

Using a multivariate Cox proportional-hazards regression model, the risk of development of ovarian cancer increased significantly with endometrioma size 9 cm or greater (HR, 5.51; 95% CI, 2.09–9.22; P = 0.031) and postmenopausal status (HR, 3.21; 95% CI, 1.79–4.69; P = 0.039). In their paper the authors advise to

manage postmenopausal women with endometriomas that were 9 cm or greater in diameter differently from younger women with smaller endometriomata.

The message I take away from this is that there is room to manoeuvre. Clearly menopausal women with large endometriomata require surgery.

Women under the age of 45 with small endometriomata (less than 5 cm?) should be offered alternative options.

The patient consent process should obviously include relevant information regarding the risk of malignant transformation, but this should be off-set against the potential impact of surgery on ovarian reserve.

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Kobayashi H, Sumimoto K, Kitanaka T, et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2008; 138: 187–193.

Van Gorp T, Amant F, Neven P, Vergote I, Moerman P. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. Best Practice & Research Clinical Obstetrics and Gynaecology 2004; 18: 349–371.

UPCOMING MEETINGS in 2010

31st Annual Meeting of Japan Society of Endometriosis
16-17 January 2010
Kyoto, Japan

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

58th Annual Clinical Meeting of the ACOG
15 - 19 May 2010
San Francisco, USA

World Congress of Minimally Invasive Gynecologic Surgery
26 - 29 June 2010
Dubrovnik, Croatia

26th Annual Meeting of ESHRE
28 - 30 June 2010
Rome, Italy

14th Course in Gynaecological Endoscopy
29 - 30 January 2010
Lisbon, Portugal

ESHRE 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

32nd British Congress of Obstetrics and Gynaecology
2 - 23 June 2010
Belfast, United Kingdom

ESHRE pre-congress course: Endometriosis - how new technologies may help
27 June 2010
Rome, Italy

IFFS 20th World Congress on Fertility & Sterility
11 - 16 September 2010
Munich, Germany

COMPLETE CONGRESS SCHEDULE

GUEST EDITOR's RESEARCH DIGEST

Endometriosis, pain and ovarian cancer

Professor Liselotte Mettler
University of Kiel
Germany

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Part 1: Laparoscopic surgery, pain and endometriosis

For this review I have selected 5 papers published between August and October 2009. The first part deals with laparoscopic surgery, pain and endometriosis and the second part with endometriosis, adnexectomy and ovarian cancer.

Laparoscopic surgery for pelvic pain associated with endometriosis
Cochrane Database Syst Rev 2009;(4):CD001300

Jacobson TZ, Duffy JM, Barlow D, Koninckx PR, Garry R.

BACKGROUND: Endometriosis is the presence of endometrial glands or stroma in sites other than the uterine cavity. It is variable in both its surgical appearance and clinical manifestation often with poor correlation between the two. Surgical treatment of endometriosis aims to remove visible areas of endometriosis and restore anatomy by division of adhesions and relieve painful symptoms. OBJECTIVES: To assess the efficacy of laparoscopic surgery in the treatment of pelvic pain associated with endometriosis. SEARCH STRATEGY: For the update in July 2009 we searched the Cochrane Menstrual Disorders and Subfertility Group's specialised register of trials (searched July 2009), the Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2009), MEDLINE (1966 July 2009), EMBASE (1980 July 2009), and reference lists of articles. SELECTION CRITERIA: Randomised controlled trials were selected comparing the effectiveness of laparoscopic surgery used to treat pelvic pain associated with endometriosis, with other treatment modalities or diagnostic laparoscopy only. DATA COLLECTION AND ANALYSIS: Assessment of trial quality and extraction of relevant data was performed independently by two reviewers. MAIN RESULTS: Five studies were included in the meta-analysis, including three full papers and two conference reports. All the randomised controlled trials with the exception of Lalchandani 2003 compared different laparoscopic surgical techniques with diagnotic laparoscopy only. Lalchandani 2003 compared laparoscopic coagulation therapy with diagnostic laparoscopy and medical treatment. Three studies (Abbott 2004; Sutton 1994; Tutunaru 2006) reported the pain scores six months post operatively. Meta-analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only (OR of 5.72 95%Cl 3.09 to 10.60 ; 171 participants, three trials, Analysis 1.1). A single study (Tutunaru 2006) reported pain scores twelve months after the procedure. Analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only (OR of 7.72 95%Cl 2.97 to 20.06 ; 33 participants, one trial, Analysis 1.1). AUTHORS' CONCLUSIONS: Laparoscopic surgery results in improved pain outcomes when compared to diagnostic laparoscopy alone. There were few women diagnosed with severe endometriosis included in the meta-analysis and therefore any conclusions from this meta-analysis regarding treatment of severe endometriosis should be made with caution. It is not possible to draw conclusions from the meta-analysis which specific laparoscopic surgical intervention is most effective.

It becomes evident that laparoscopy with excision of endometriotic lesions relieves pain and is superior to diagnostic laparoscopy only. It is really a question of why doctors are still trying to avoid the excision of endometriotic lesions linked to pain.

What can be done from our side to convince them to either send the patients to surgical centres or treat them properly? Incomplete surgery can cause a lot of pain.

Endometriosis of the diaphragm: four cases treated with a combination of laparoscopy and thoracoscopy
J Minim Invasive Gynecol 2009;16(5):573-80.

Nezhat C, Nicoll LM, Bhagan L, Huang JQ, Bosev D, Hajhosseini B, Beygui RE.

STUDY OBJECTIVE: We aim to describe the clinical characteristics and the principles of combined laparoscopic and thoracoscopic management of women with diaphragmatic endometriosis at our institution. DESIGN: Case series (Canadian Task Force Classification II2). SETTING: Tertiary care referral center. PATIENTS: Four women with diaphragmatic endometriosis. INTERVENTIONS: Laparoscopy and thoracoscopy. MEASUREMENTS: We retrospectively reviewed the charts of 4 consecutive women with diaphragmatic endometriosis who underwent laparoscopy and thoracoscopy from June 2008 through September 2008. MAIN RESULTS: Four patients underwent a combination of laparoscopy for treatment of abdominopelvic endometriosis and thoracoscopy for treatment of diaphragmatic endometriosis. All patients had a history of chest pain. Three had a history of pelvic pain. Two had a history of catamenial hemothorax or pneumothorax. Two had been previously diagnosed with endometriosis, and three had a history of hormonal pharmacotherapy. All underwent laparoscopy and thoracoscopy without complications. All had uneventful recoveries. At nine-month follow-up, all patients were free of chest pain, and one patient had recurring pelvic pain. CONCLUSIONS: To the best of our knowledge, this constitutes the only reported series of patients with endometriosis who underwent a procedure systematically combining both laparoscopy and thoracoscopy for treatment of abdominopelvic and thoracic disease. It confirms that combined laparoscopic and thoracoscopic diagnosis and management of diaphragmatic endometriosis is reasonable. The inferior aspect of the diaphragm should be evaluated in all patients undergoing laparoscopy for endometriosis. Concomitant thoracoscopy should be considered for all patients with history of catamenial hemopneumothorax, cyclic chest or shoulder pain, or cyclic dyspnea. The aim of treatment should be to remove endometriotic lesions, to provide symptomatic relief, and to avoid recurrence. The use of these minimally invasive techniques may reduce the need for laparotomy or thoracotomy in affected patients.

The relatively rare location of endometriosis on the diaphragm produces severe chest pain with hemothorax or pneumothorax.

The combined endoscopic management with an abdominal and thoracic approach appears helpful in these rare cases.

Surgeons have to think about the possibility of multidisciplinary collaboration in the treatment of these patients. It is important to realise that selective treatment of individual specialities may only lead to partial success.

Oxidative stress status in normal ovarian cortex surrounding ovarian endometriosis
Fertil Steril 2009 Oct 9 [Epub ahead of print]

Matsuzaki S, Schubert B.

Expression levels of 8-hydroxydeoxyguanosine, a sensitive indicator of DNA damage resulting from oxidative stress, were significantly higher in samples of normal ovarian cortex surrounding endometriotic cysts when compared with ovarian cortex surrounding dermoid and serous ovarian cysts. These findings suggest that the normal ovarian cortex surrounding endometriotic tissues is more severely affected by oxidative stress than ovarian cortex adjacent to other benign ovarian cysts.

Very often ovarian cysts are left to grow after being recognised by a gynaecologist for several months. This, however, is damaging the ovarian cortex surrounding the endometriotic tissue as proved by oxidative stress. While these ovarian cysts mostly do not lead to severe pain situations in some cases smaller cysts cause pain and have to be resected.

All three papers described in part 1 of this Editorial Digest focus on pain and the damaging effects on endometriosis.

Part 2: Endometriosis, adnexectomy and ovarian cancer

Endometriosis and ovarian cancer: A review
Gynecol Endocrinol 2009 Aug 28 [Epub ahead of print]

Vlahos NF, Kalampokas T, Fotiou S.

Objectives. To describe the relationship between endometriosis and ovarian cancer. Search strategy. Review of the relevant clinical, epidemiologic, and molecular biology literature. Selection criteria. Studies published in the English language using the MEDLINE database. Data collection and analysis. Relevant studies were reviewed by the three authors and those that seem to be of significant scientific value, based on the methodology and statistical power, were included. Main results. Endometriosis and ovarian cancer share many common predisposing factors. Both conditions demonstrate similar patterns regarding local invasion and distal spread they respond similarly to estrogen-induced growth signaling, they express resistance to apoptotic mechanisms and they are characterized by genomic instability. Endometrioid and clear-cell are the most frequent types of ovarian cancer associated with endometriosis. Tubal ligation, in women with endometriosis, seems to prevent retrograde menstruation but it has also been shown to be protective from these types of ovarian cancer. Conclusion. There is evidence to support that endometriosis (by definition a benign process), could simultaneously have the potential for malignant transformation. More studies are needed to establish risk factors that may lead to malignant transformation of this condition and to identify predisposed individuals who may require closer surveillance.

As endometriosis and ovarian cancer have common features, it is of utmost importance to excise recurrent endometriotic lesions and not rely on their benign character. All the discussions in reproductive medicine arguing against surgical intervention for endometriotic cysts ignore the danger of malignant transformation of endometriotic tissue into ovarian cancer.

Should the ovaries be removed or retained at the time of hysterectomy for benign disease?
Hum Reprod Update 2009 Sep 30 [Epub ahead of print]

Hickey M, Ambekar M, Hammond I.

BACKGROUND Bilateral oophorectomy is commonly performed at the time of hysterectomy for benign disease. Indications for oophorectomy vary, but in most cases relatively little high-quality information is available to inform the surgeon or patient regarding the relative risks and benefits of ovarian conservation or removal. This review will address the common clinical situations when oophorectomy may be performed and will evaluate the evidence for risk and benefit in each of these circumstances. The aim of this review is to bring together the evidence regarding oophorectomy in pre- and post-menopausal women and to highlight the areas needing further study. METHODS We searched the published literature for studies related to outcomes following surgical menopause, risk-reducing surgery for ovarian cancer, surgical treatment for endometriosis, bilateral oophorectomy for benign disease and treatment for premenstrual syndrome/premenstrual dysphoric disorder. RESULTS Rates of oophorectomy at the time of hysterectomy for benign disease appear to be increasing. There is good evidence to support bilateral salpingoophorectomy (BSO) as a risk-reducing surgery for women at high risk of ovarian cancer, but relatively little evidence to support oophorectomy or BSO in other circumstances. There is growing evidence from observational studies that surgical menopause may impact negatively on future cardiovascular, psychosexual, cognitive and mental health. CONCLUSION Clinicians and patients should fully consider the relative risks and benefits of oophorectomy on an individual basis prior to surgery.

The old question whether to remove the ovaries at hysterectomy becomes particularly relevant when thinking about endometriosis and ovarian cancer. As the transformation rate from endometriosis into ovarian cancer has to be considered being greater than 2 %, ovaries that show any endometriotic lesions should be removed at the time of hysterectomy. Only if the ovaries show no pathology at all is it advisable to retain these organs till the age of 65 years.

Endometriosis shows new variants every time we deal with the disease and keep the doctor continuously alert. Let us not get tired to look for new solutions.

Meet the WCE2011 team

The 11th World Congress on Endometriosis will be in Montpellier, France, from **4 – 7 September in 2011.**

In this issue we take the opportunity to introduce you to the local organising team, which is busy preparing an exciting programme with the latest news in science and clinical practice within our field. The congress theme will be **excellence** in all that is done in endometriosis!


Professor Bernard Hédon

The president

Heading up the team is Professor **Bernard Hédon**, who was also the president of the 15th IFFS World Congress on Fertility and Sterility, which was held in Montpellier in 1995.

Professor Hédon graduated in Medical Science from Montpellier University Medical School, France in 1974, where he became professor in obstetrics and gynaecology in 1985, head of the division of reproductive medicine, and then head of the department of obstetrics-gynaecology and reproductive medicine at A. De Villeneuve Montpellier University Hospital in 1993. He has also been a member of the scientific and administration committees of Montpellier Medical School and Montpellier University, as well as the president of the Montpellier Academic Hospital Medical Council.

An active member in many societies in France, Professor Hédon was a founder of the GEFF (Groupe d'Etude de la Fécondation en France) and served as its General Secretary from 1988 up to 1994. He served also as president of the French Fertility Society, and of the French Federation. He was the secretary general of IFFS for six years before being elected president – where he focused his efforts on education.

Professor Hédon has authored many scientific contributions published in the French and in the international literature. His works have been on the clinical approach of human fertility and, more specifically, on the Fallopian tubes, endoscopy and surgery, including microsurgery, and in vitro fertilization. In endometriosis his work has specifically focused on the clinical management in infertile patients.

The congress coordinator

Anne-France Puech, is the congress coordinator for WCE2011 and represents the professional congress organisers MCI.


Anne-France Puech

She has 15 years of experience in congress organisation.

Ms Puech attended Montpellier Superior Business School, and then began her career in 1986 with the organisation of the Euromedicine Show, an event initiated by Montpellier city which gathered 12,000 healthcare professional every year for a decade.

Since 1997, she has been in charge of the development of PCO AMS and responsible for more than 50 national or international congresses. Since the merger of AMS and MCI, Anne-France Puech benefits from the expertise of an international event communication leader that delivers events from 20 to 20, 000 participants all over the world.

MCI France has 85 employees in its four offices located in Paris, Lyon, Montpellier and the French Riviera. MCI Group is present through 37 offices in 20 countries and employs more than 850 people worldwide.


Professor Hervé Dechaud

The local organising committee

Professor **Hervé Dechaud** is the medical director of the department of reproductive medicine and surgery at the University Hospital in Montpellier, France.

Professor Dechaud received his medical degree in 1996 in obstetrics and gynaecology. He completed his PhD at Montpellier University in tubal infertility and impairment of embryo implantation, and subsequently went to the University of Texas, Health Science Center at San Antonio, Texas, USA as a research fellow in 1999.

His research interests include endometrium and embryo implantation, infertility related to endometriosis, and ovarian hyperstimulation protocols for assisted reproduction cycles.

At the present time, he is the medical director of the department of reproductive medicine and surgery at the University Hospital in Montpellier, France.


Dr Lionel Reyftmann

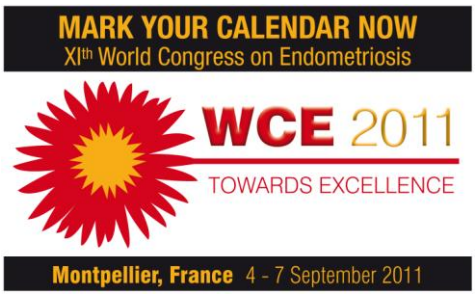
Dr **Lionel Reyftmann** was born in Paris in 1971, and studied medicine, then obstetrics and gynaecology at the Montpellier School of Medicine under the guidance of Professors Hédon and Dechaud.

He qualified as a medical doctor in 2003 and then as a certified reproductive medicine Specialist in 2007.

Dr Reyftmann's particular interests are reproductive surgery, especially in the field of endometriosis and mild ART in poor responders. He has co-authored 25 peer reviewed papers.

He supports the idea that the World Congresses and the platform which the World Endometriosis Society provides are wonderful opportunities to meet clinicians and scientists from all around the world.

As a matter of fact, Dr Reyftmann loved WCE2008 so much that he plans to go back to Australia for a fellowship in laparoscopic surgery!



Keep up to date at:
www.wce2011.com

COMMENTS and DEBATE

We welcome your input!

The e-Journal is a key medium for WES members to "stay in touch" in between the world congresses. We wish to encourage everyone to feed back with their comments to articles published in the e-Journal – to share their opinions and experiences, so that results can continuously be built upon to further our cause. Debate is healthy, so don't be shy!

You contribution can be sent to the editor at: **ejournal-editor@endometriosis.org**

The deadline for the next issue is 26 January 2010.