



Professor Rodolphe Mabeux
President WES

Join us to stay tuned!

The World Endometriosis Society is a non profit society registered in Canada with a mission to “foster research and promote the exchange of information”, through:

- promoting the exchange of clinical experience, scientific thought and investigation among gynaecologists, endocrinologists, scientists, biologists and other qualified individuals interested in advancing the field of endometriosis
- fostering research in endometriosis pathogenesis and treatment
- disseminating information about endometriosis
- encouraging and supporting collaboration among national and international societies interested in endometriosis.

Initially, the Society was set up to serve as a platform of collaboration between the World Congresses on Endometriosis (WCE), but at our last meeting in Maastricht, we decided to become more active!

To do so, we have started a profound transformation of our Society during the last few months. Our head office has been moved from Montreal to London. It is now under the responsibility of Lone Hummelshoj of www.endometriosis.org. We have set up with the Royal Bank of Canada a secure platform for online membership payment. When you pay your dues on our internet site, you are automatically redirected for payment with a credit card to the site of the Royal Bank of Canada. Please, renew your membership as soon as possible; your contribution makes a significant difference to the work of the Society, and the support we are able to provide to our members. To do so, just visit our site now by double-clicking on our internet address: <http://wes.endometriosis.org/join.htm> and follow the instructions for membership renewal.

We are also working on establishing a foundation to promote a better understanding of this pathology; an initiative I will be able to tell you more about in the next issue of the e-Journal. Stay tuned!

For the WES e-Journal, Dr Ali Akoum has accepted to continue as editor for another 3-year term. This e-Journal, started in June 2000, was probably one of the first initiated by an international society to communicate with its members. During the next 3 years Dr Akoum will focus on research and new developments but also present review articles on important topics. We always welcome contributions from our members!

The WCE is the main source of revenues for the WES, and as you know the last WCE was a real success. A profit of more than C\$ 40,000 truly enables us to enhance our activities to the benefit of our members (again: many thanks to Hans Evers and his great team from The Netherlands!). We wish to keep this momentum going: so, please mark your calendars with 11 – 14 March 2008. These are the dates when our Australian colleagues are preparing for us a fantastic meeting in Melbourne for our 10th WCE. Australia is a superb country and the WCE is the best forum to stay informed on the recent advances on endometriosis.

Join us!

Sincerely,

Rodolphe Mabeux

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EDITOR'S MESSAGE



*Professor Ali Akoum
Editor, WES e-Journal*

Dear colleagues –

I'm honoured to take over the e-Journal for another 3-year term. We see in the e-Journal a valuable tool to help achieving our society's objectives of disseminating information on endometriosis, promoting exchange of ideas, encouraging collaborations and creating connections between scientists, clinicians and all individuals who are dedicated to expand knowledge and to improve endometriosis diagnosis and treatment for the patients' well-being.

You are invited to use the e-Journal as a vehicle of your thoughts, opinions, and questions and to stay tuned, as highlighted by our president Rodolphe Maheux. This is an opportunity to get your message to reach all WES members!

During the last year we brought several changes to the e-Journal with the object of providing you with high quality information about endometriosis. In each issue, we now regularly have at least two scientific papers: a special guest editorial and a review article. In this issue, Dr Thomas D'Hooghe *et al* provide us with an interesting opinion/review article highlighting endometrial-peritoneal interactions in endometriosis. There is still limited knowledge regarding early endometrial-peritoneal crosstalk, and it is quite possible that not only endometrium but also peritoneum is an active player. This is no doubt an interesting avenue of research. In the second article, Dr Eduardo Schor provides us with an interesting literature review of the role of environmental factors, especially dioxin, a potent endocrine disrupter, in endometriosis pathogenesis. I thank the authors for their appreciated contribution and we are looking forward to receiving your feedback to these articles, or to any other issue that may stimulate debate and trigger constructive exchange of views and ideas.

Contact us and get aboard!

Cordially,

Ali Akoum

NEWS ROUND UP

[New law in Spain allocates more money to investigate endometriosis](#)

The Spanish Congress of Representatives has unanimously approved the allocation of more money to the fight against endometriosis following a proposal of law instigated by Asociacion de Endometriosis Española.

[Endometriosis is recognised in the Council of the European Union's conclusions on women's health](#)

Following the informal meeting between health ministers in all European Member state in Vienna in April this year, the Council of the European Union has formally recognised the need that more attention is given to women's health issues - and endometriosis is again highlighted as a disease which deserves specific attention.



Rodolphe Maheux and Lone Hummelshoj

[Strategic plan emerging for the WES](#)

WES president Rodolphe Maheux and Secretary General Lone Hummelshoj met on a hot summer's day in London in June to sit down and get a strategic plan together for the next year for the Society. They are "fired up" and feel the Society is in good shape and hope that everyone who are serious about endometriosis will join us in our efforts to increase global collaboration in this field.

[Change in WES Council](#)

It is with regret that we announce the resignation from the WES Council of Agneta Bergqvist. She has taken up a position as a part-time employee with Pfizer to advise them on urology and women's health, including endometriosis. Says Agneta Bergqvist: "It has been a great pleasure to be a member of the Council since the creation of WES and to be the first women on the Council! I congratulate you for the exciting and promising development of the Society and wish the Society all success in the important mission to expand the knowledge, understanding and care of endometriosis". Rodolphe Maheux responds: "I would like to formally thank Agneta Bergqvist for her contribution to the Society. Agneta remains in the field of endometriosis and will no doubt continue to contribute to our collaborative efforts to get to the bottom of this disease".

Endometrial-peritoneal interactions and endometriosis

Kyama CM^{1,3}, Mibalyi A¹, Simsa P^{1,4}, Falconer H², Fulop V⁴, Mwenda JM³, Peeraer K¹, Meuleman C¹, D'Hooghe TM^{1,3}

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The natural history and spontaneous evolution of endometriosis is still shrouded in the mist of intricate puzzle and the current efforts to study these phenomena are staggering to envisage, but an area of great interest. Although the aetiology is not precisely known, endometriosis is suggested to result from refluxed endometrial cells into the peritoneal cavity during menstruation [Sampson 1927]. However, there is still limited information available regarding the early endometrial-peritoneal attachment and invasion process in the development of peritoneal endometriosis, mostly from *in vitro* studies [Witz *et al* 1999, Debrock *et al* 2002, Debrock *et al* 2004, Groothuis *et al* 1999, Debrock *et al* 2006]. To study how endometriosis evolves, it is important to understand the biology of the two tissues involved and how they interact with each other before the transition of endometrium to endometriosis occurs.

Endometrium is a unique adult tissue that undergoes a proliferation and secretion followed by menstruation [Jabbour *et al* 2006, Tabibzadeh 1996, Osteen *et al* 2002] leading to re-growth of functional endometrium during the menstrual cycle. It is not clear how endometrium has the capacity to survive outside the uterine cavity and how it can implant leading to the development of endometriosis. The peritoneum on the other hand is a single layer of mesothelial cells underlying extracellular matrix of connective tissue with fibroblasts, collagen fibres, adipocytes, leukocytes and blood vessels [Witz *et al* 1998].

The current assertion is that successful development of endometriosis requires endometrial cells to adhere to mesothelium and to invade the extracellular matrix. This theory suggests that the peritoneum may function as a "passive recipient" for ectopic tissue attachment, and is supported by previous *in vitro* studies [Witz *et al* 1999, Witz *et al* 2001]. However, other investigators have reported that the mesothelium acts as a barrier to the attachment of endometrial cells and have proposed that trauma or injury to the peritoneum is required for endometrial-peritoneal adhesion [Van der Linden *et al* 1996, Groothuis *et al* 1998].

The development of endometriosis is hypothesised to be a complex process, which may be facilitated by several factors, including the cytokines, growth factors and quality of endometrial cells. It has been suggested that the expression of adhesion molecules like integrins on the surface of mesothelium may play a role in the initial attachment of endometrial cells to peritoneum [Witz *et al* 1998]. Macrophage derived cytokines may also contribute

to the development of endometriosis by promoting neovascularisation and attachment of endometrial cells to the peritoneum [Wieser *et al* 2002, Harada *et al* 2001]. Increased angiogenesis is reported to be common around the peritoneal explants and increased angiogenic activity has been observed in peritoneal fluid (PF) of women with endometriosis [Nothnick 2001]. It is not clear to which extent these phenomena are endometrium-dependent or peritoneum-dependent.

An active role for the endometrium in endometrial-peritoneal attachment and invasion has been supported by the significant biological differences in eutopic endometrium between women with and without endometriosis. However, few investigators have compared the biological properties of menstrual endometrium between women with and without endometriosis.

In a recent study [Kyama *et al* 2006a] we reported increased menstrual endometrial mRNA expression of α_v integrin, the combined $\alpha_v\beta_3$ integrins in women with endometriosis when compared with controls. During the luteal phase, endometrial mRNA expression of IL-1 β and RANTES was increased in women with endometriosis when compared with controls [Kyama *et al* 2006a]. During the menstrual or luteal phase, endometrial mRNA expression of aromatase was higher in women with endometriosis when compared to controls [Kyama *et al* 2006b].

At present, it is clear that not only endometrium but also macroscopically normal peritoneum taken outside the pelvic brim is an active player and not a passive recipient in the development of endometriosis, especially during menstruation [Kyama *et al* 2006a and 2006b].

Firstly, during the menstrual phase, peritoneal expression of IL1- β , ICAM-1, TGF- β and IL-6 mRNA is up-regulated in women with endometriosis when compared with controls [Kyama *et al* 2006a and 2006b].

Secondly, in women with or without endometriosis, the expression levels of mRNA for aromatase (luteal phase only) and for VCAM-1 are lower in endometrium than in peritoneum [Kyama *et al* 2006a].

Thirdly, we demonstrated increased peritoneal mRNA expression of TNF- α and MMP-3 in endometriosis women when compared with controls during the luteal phase [Kyama *et al* 2006b].

Fourthly, in women with endometriosis, peritoneal mRNA expression of RANTES and VCAM-1 are significantly higher during the menstrual phase when compared to the luteal phase [Kyama *et al* 2006a].

These observations may have important implications regarding endometrial-peritoneal interactions. *In vitro* studies have shown increased endometrial stromal cell adhesion to mesothelial cells pretreated with TNF- α [Zhang *et al* 1993]. Similarly, *in vitro* incubation of endometrial stromal cells with increasing concentrations of IL-8 has been reported to stimulate their adhesion to fibronectin [Garcia Velasco *et al* 1999]. Also *in vivo* adhesion of human endometrial cells to mouse peritoneum was moderately increased by treatment with TNF- α and IL-6 [Beliard *et al* 2003].

In contrast in a recent study, TNF- α , IL-8 and IL-6 failed to stimulate, *in vitro* adhesion between endometrial epithelial cells and mesothelial cells in a dose dependent fashion [Debrock *et al* 2006]. After attachment,

endometrial cells invade the extracellular matrix, a process influenced by matrix metalloproteinases (MMPs), a group of enzymes important in the control of extracellular matrix turnover [Bruner *et al* 1999]. MMPs are up-regulated by TNF- α and IL-1, which could partly explain the increased invasiveness of endometrial fragments in women with endometriosis [Sillem *et al* 2001].

In conclusion, recent evidence has shown increased expression of inflammatory cytokines, aromatase and adhesion factors in endometrium and in macroscopically normal peritoneum from women with endometriosis compared to controls during the menstrual or luteal phase [Kyama *et al* 2006a and 2006b].

Both endometrium and macroscopically normal peritoneum are affected by profound biological changes dependent on the phase of the menstrual cycle and on the presence or absence of endometriosis. The time has come to define endometriosis not only as an endometrial disorder but also as a peritoneal disease.

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SPECIAL RESEARCH ANNOUNCEMENT

Standardising the Measurement of Pain and Diagnostic Criteria in Endometriosis

An NICHD and NIH Conference on the topic of "Standardising the Measurement of Pain and Diagnostic Criteria in Endometriosis" will take place on **20 October 2006** (the day before the start of the ASRM) in New Orleans, USA.

The aim of this meeting is to achieve a consensus regarding the most appropriate entry criteria, outcomes and measurement tools for clinical studies assessing treatments for endometriosis associated pain.

The organisers, Pamela Stratton (USA) and Stephen Kennedy (UK) encourage participation by clinicians and scientists in the fields of chronic pelvic pain, endometriosis and pain in general, as well as representatives from the pharmaceutical industry, the American Society of Reproductive Medicine, the FDA, and patient advocacy groups.

For more information and to reserve a place please go to: <http://endometriosis-conference.nichd.nih.gov>

REVIEW ARTICLE

A literature review of the connection between dioxin exposure and endometriosis

Eduardo Schor

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Introduction

Despite the numerous papers published over the last decades, pathogenesis of this enigmatic disease, called endometriosis, still remains obscure. Immune alterations, disorders of the topical endometrium and genetic disposition have all been associated with the genesis of the disease.

At present we seem to observe an increasing prevalence, in addition to a greater aggressiveness of endometriosis, and thus a probable involvement of environmental factors has been hypothesised.

Dioxins are a group of environmental pollutants consisting mainly of PCDF, PCB and PCDD. Among PCDDs 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), usually known as dioxin, one of the most potent pollutants, is to be noted, and there is evidence suggesting that this compound may be related to endometriosis (for additional information on dioxin see www.ejnet.org/dioxin/).

Dioxin is a universal pollutant, derived mainly from incineration of garbage and metal processing. Because it is lipophilic it is retained in the food chain and common foods are the main source of dioxin exposure for humans.

TCDD, an endocrine disruptor, may lead to endometriosis mainly through genomic mechanisms, however, non-genomic actions have been reported. Its action on DNA, as well as on sexual steroid synthesis and metabolism, may lead to alterations which formerly had already been related to endometriosis.

Mechanisms of action of dioxin

Dioxin activity in the body is by binding to the aryl hydrocarbon receptor after which the compound is carried to the nucleus by the AHR nuclear translocator (ARNT) where it will bind to the dioxin responsive element activating the transcription of a series of genes [1].

One of the principal defense mechanisms of the body against the xenobiotic is activation of genes that code for detoxification enzymes, mainly those of the first phase with emphasis on the Cyp family, especially Cyp 1A1 and Cyp 1B1 [2].

Numerous genes, responsible for the transcription of pro-inflammatory cytokines, are activated after exposure to dioxin and among which RANTES, IL-5, IL-6, IL-7, IL-9, IL-10 and IL-1 β , TNF-alpha should be mentioned. The vascular endothelial growth factor (VEGF), which is

known to be involved in the pathophysiology of endometriosis, has also its transcription activated by dioxin. Binding of ARNT to DNA also leads to activation of transcription of genes responsible for oestradiol synthesis besides, possibly, altering splicing in the transcription of the gene responsible for coding for progesterone receptors [3,4,5].

Dioxin and endometriosis

In view of the evidence that dioxin could be involved in oestrogen-dependent diseases, some authors evaluated the association of this pollutant with the disease. Rier *et al*, in 1993 [6], evaluated the prevalence of endometriosis in female rhesus monkeys exposed to dioxin for 10 years. The authors observed a significant and dose-dependent increase in the prevalence of moderate and severe endometriosis in animals exposed to the pollutant. On studying cynomolgus monkeys, Yang *et al* [7] reported, in addition to persistence of lesions, an increase in their diameter after exposure to TCDD when compared to non-exposed animals.

In humans, population studies in Seveso, Italy, and in Belgium, at sites where there was exposure of the population to high doses of the pollutant because of industrial accidents, failed to identify the relationship between an increase in serum dioxin concentration and the prevalence of endometriosis. However, due to the fact that dioxin accumulates in fatty tissues, serum measurement would not be the ideal means to estimate dioxin concentration present in the body.

Reviewing the literature, Arisawa *et al* concluded that there is no evidence up to now supporting the hypothesis of a relationship between the disease and exposure to dioxin but emphasize the need for population studies of high statistical power in order to be able to evaluate this association [8].

Role of dioxin in the pathogenesis of endometriosis

Studies on the pathogenesis of endometriosis report alterations in the topical endometrium. Disturbances of the cell cycle, either increase in proliferation or decrease in apoptosis, have already been reported. Increase in matrix metalloproteinase expression, as well as decrease in TIMP, favour implantation of this endometrium in the peritoneal surface. After implantation, formerly described increase in VEGF is responsible for neo-angiogenesis.

All these alterations favour implantation of endometrial cells in an inhospitable environment: the peritoneum [9].

On looking for a single alteration which leads to all these disturbances it was discovered that progesterone regulates, either directly or indirectly, their expression in the topical endometrial cells, presupposing that a deficiency in the action of this hormone could be involved in the genesis of endometriosis.

Progesterone acts on two different receptors coded for by the same gene, PRA and PRB, and an adequate proportion between both is fundamental for the correct action of progesterone on the endometrium. The known anti-oestrogenic action of progesterone is mediated by the type B receptor; when there is an increase in PRA or a decrease in PRB, we could have an oestrogen-like action, favouring the emergence of endometriosis. Igarashi *et al* recently reported a decrease in the PRB/PRA ratio in cultured topical endometrial cells of women with endometriosis after exposure to dioxin, suggesting that alteration in progesterone action and consequently the previously reported disturbances in the topical endometrium of women with endometriosis would be due to exposure to TCDD [10].

In addition to the endometrial alterations, dioxin acts by increasing the expression of detoxification enzymes. Increase in the expression of the Cyp family enzymes, mainly Cyp 1A1, leads to a paradoxical effect; this enzyme metabolises oestrogens to catechol-oestrogens, generating a strongly oestrogenic environment, contributing to the pathophysiology of the disease. Finally, several immune alterations in the peritoneal environment of patients with endometriosis, either in the humeral or in the cellular compartment, have already been described, alterations that are necessary for the endometrial cell which reaches the pelvic cavity not to be removed. Dioxin acts on a series of components of the immune system; we may point out the decrease of NK cell action, in addition to stimulation of secretion of pro-inflammatory cytokines such as IL-5, IL-6, IL-9 and RANTES.

Alterations promoted by exposure to this environmental

potent pollutant could lead to disorders of the topical endometrial cells, a hyper-oestrogenic environment and immune alterations which all together would lead to the emergence of endometriosis.

Genetic polymorphisms

In the beginning of the 1980s of the last century some studies described that retrograde menstruation occurred in approximately 80% of women, thus showing that the theory of retrograde menstruation proposed by Sampson did not explain alone the genesis of the disease; the same occurring with the environmental theory. Dioxin is an ubiquitous pollutant and all women, in a same environment, are exposed to the same dioxin concentration. What is the reason why only a part of them develops the disease?

This fact is justified by genetic polymorphisms which are small DNA alterations that in the presence of an external stimulus generate phenotypic alterations. Diverse polymorphisms have already been studied in women with endometriosis, among which detoxification enzymes of the first and second phases are to be pointed out as concerns dioxin. Up to the present the results were inconclusive. In a review of the literature, Guo analyzed studies on polymorphism of Cyp 1A1 and 1B1 first phase enzymes, GSTM of the second phase and reached the conclusion that new population studies are required to define if there is or not alteration of the genes coding for detoxification enzymes in women with endometriosis [11].

Conclusion

The actual role of dioxins in the pathogenesis of endometriosis is still being discussed and evidence suggests that endometrial, immune alterations may originate from exposure to this xenobiotic. Genetic alteration, probably the polymorphisms, would be the cause of the disease's emergence in only a part of the exposed women, however further studies on these alterations in genes that code for detoxifying proteins are still needed.

The search for pathogenetic mechanisms of endometriosis should be unremitting since the elucidation of the mysteries of this enigmatic disease is mandatory for the improvement of therapy as well as primary prevention.

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NEW BOOKS



[The challenge of reproductive medicine at Catholic Universities: time to leave the catacombs](#)

edited by Ivo Brosens

New technologies, developing at an unbelievable pace, have profoundly changed many areas of reproductive medicine including fertility control, infertility treatment, embryology, prenatal diagnosis and foetal surgery.

However, contraceptive techniques, assisted reproductive technologies, pre-implantation genetic diagnosis and embryonic stem cell research are deeply dividing Catholic universities around the world. Is modern reproductive medicine based on personal ethics and practiced at progressive Catholic universities compatible with the Catholic doctrine?



[Handbook of hormonal contraception and office gynecology](#)

by Rodolphe Maheux

This user friendly and comprehensive guide belongs on the desk of every practicing health care professional.

The handbook is designed to help physicians steer their female patients successfully through the reproductive cycle from adolescence through menopause, providing straightforward answers to the questions women most often ask their doctors, including pelvic pain and endometriosis.

It has check lists and practical tips throughout – and has been designed to slip easily into the pocket of a lab coat!

UPDATE ON WCE 2008

10 Aussie traditions

David Healy MD, President WCE 2008

I am writing this from the only country that regularly eats its national symbols. Yes - things are different here! Even to arranging a World Congress for the WES through the Australian Gynecological Endoscopy Society. Here are 10 Aussie congress traditions to help you prepare for WCE in 2008:

1. Accountability

Like Admiral Horatio Nelson, we expect every (wo)man to do their duty: to do one task well for WCE 2008. The WES Board will lead us all, but everyone can at least register a friend - or bring the kids for the holiday of a lifetime!

2. Website

The programme announcement will go out in February 2007 by mail – however, the preliminary programme is already available on our website www.wce2008.com

3. Social events are compulsory!

The opening ceremony, dinners, and the closing congress banquet are all opt-in activities. This is because Australia has so few people. Costs are included in the registration, and there are no refunds! We will make sure you have a great time.

4. Patients are everywhere

Patients are always welcomed and a part of our congresses at all session. See 1, 2 and 3 above.

5. Scientists, trainees and nurses

See 1, 2, 3 and 4 above.

6. Leadership

Ever wondered who is actually on the WES board? Now you will find out! Each WES board member will have visible duties each morning, afternoon and evening, so you will get to see your leadership in action! Come and get their autographs!

7. We start on time and we end on time

The programme chairmen are building a fantastic programme for you. For it to work, it must start on time, and we must stick to time.

8. Book early – book often

Did I mention the programme will be out in February 2007? Please help us help you by registering and paying early.

9. Posters

Aussie tradition is that you speak beside your poster for your two minute “message”. Your audience will at all times include at least one WES board member, who questions you for 3 minutes, and then marks and ranks your work.

10. Prizes

To win your well-deserved prize at WCE 2008 you must be there in person to receive it. Otherwise the WES board shall award the next ranked poster, etc. No show = no prize (and no correspondence will be entered into). All prizes are announced at the pre-banquet closing ceremony.



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RESEARCH HIGHLIGHTS

[Molecular genetic evidence that endometriosis is a precursor of ovarian cancer](#)

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UPCOMING MEETINGS

[1st Argentinean Congress on Endometriosis](#)

21 - 22 September 2006
Buenos Aires, Argentina

[2nd Hellenic Endometriosis Congress](#)

24 - 26 November 2006
Crete, Greece

[FULL CONGRESS SCHEDULE](#)

[VIIth PAX meeting](#)

28 - 30 September 2006
Leuven, Belgium

[IFFS 19th World Congress on Fertility and Sterility](#)

29 April - 3 May 2007
Durban, South Africa