



# Newsletter

## World Endometriosis Society

Issue No. 2

Fall 1999

### Message from the President

I am pleased to present you with this Second Newsletter and to announce that the development of the Society is proceeding with great success.

It was unanimously agreed by Council that all future WES presidents should contribute a "Presidential Initiative" and I am pleased to inform you that as my initiative, WES will be producing an educational CD-rom, "How to diagnose Endometriosis," which will be distributed at the London 2000 WES congress. Special gratitude to Zeneca for providing the financial support necessary for the production of this CD-rom.

The WES Council convened on two separate occasions (during IFFS/ASRM in San Francisco and during the GnRH

Conference in Geneva). See update from the Executive Secretary for a report on the highlights discussed at these Council meetings.

Be sure to mark your calendar for the WES 2000 Congress -- see special article in this issue about this congress. You will also find registration materials enclosed.

A special note of gratitude to Paolo Vercellini for his enlightening article in this issue on Endometriosis around the World.

Professor Jacques Donnez, MD  
President, WES

#### World Endometriosis Society

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### IN THIS ISSUE

|   |         |
|---|---------|
| Society Update from Executive Secretary       | ..... 2 |
| Endometriosis Around the World                | ..... 2 |
| ● Pathogenesis: anatomical factors            | ..... 2 |
| ● Pathogenesis: genetic factors               | ..... 3 |
| ● Diagnosis                                   | ..... 3 |
| ● Medical Treatment for Infertility           | ..... 6 |
| ● Surgical Treatment                          | ..... 6 |
| ● Pathogenesis of pain                        | ..... 7 |
| ● Surgical Treatment for stage III/IV disease | ..... 7 |
| WCE London 2000                               | ..... 4 |
| WES goes Digital                              | ..... 6 |
| Call for Bids Xth WCE 2006                    | ..... 8 |
| Future Venues                                 | ..... 8 |

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This is gratefully acknowledged by the World Endometriosis Society

To enquire about the possibilities of sponsoring issues of the WES Newsletter, or advertising, please contact Rodolphe Maheux at: World Endometriosis Society, 10, rue de l'Espinay, D1-719, Québec, QC, Canada G1L 3L5. Tel.: (418) 525-4443, Fax: (418) 525-4481, e-mail: endo2world.fmed.ulaval.ca



World Endometriosis Society

## Update from Executive Secretary

I am pleased to report on the following items from the recent WES Council Meetings:

- The sixth WES Congress in Québec City attracted 825 delegates and had a surplus of \$80,000 Cdn. part of these funds have been used to establish WES.
- The World Endometriosis Society was incorporated in Canada with a federal charter on November 1, 1998.
- The by-laws of the Society were unanimously approved by the Council and are included with this newsletter.
- A copy of the Wes membership form is also included with this newsletter. If you are already a WES member, please pass this on to a colleague.
- WES participated in the IFFS/ASRM 1998 Congress as a non-profit exhibitor in order to raise awareness of the Society and to begin to recruit new members. The First Announcement of the London 2000 Congress was distributed at this booth, along with the WES First Newsletter and extra copies of the Abstract Volumes from the Québec City Congress.
- WES Goes Digital!  
The web site courtesy of Obgyn.net is a very effective tool for the Society to reach new members. Requests for information on becoming a WES member are received regularly. Soon you will be able to join WES or pay for your membership through the web site at: <http://worldendo.obgyn.net/>

This service to be implemented over the summer, will allow registrants of future WES congresses to select their program via e-mail. Payment of society dues and application for membership to the Society will be facilitated to allow the Society to keep the high cost of paper, printing and mailing from devouring the budget, as it does for most young societies.

As our membership is distributed around the world, the Internet and e-mail are the only logical solutions to our member's information needs. WES has a history of mutual collaboration with Obgyn.net and we are pleased to be the first society to offer these advantages to our members. Who knows where it will all end up but live Internet broadcasts from WCE 2000 sessions are a definite possibility.

Be sure to check out the WES web site at <http://worldendo.obgyn.net/>

**Rodolphe Maheux**  
*Executive Secretary, WES*

## Highlights in Endometriosis Around the World



The objective of this new section of the WES newsletter is to consider recently published studies regarding different aspects of endometriosis. They are briefly introduced, the results summarized and, when opportune, the most important points commented, the consequent practical implications defined, and the unsolved aspects needing further research described. The studies were selected by Paolo Vercellini based on the relevant English-language literature between June 1998 and May 1999 identified through MEDLINE and EMBASE.

### Pathogenesis: anatomical factors

Although most experts believe that retrograde menstruation represent a key factor in the pathogenesis of endometriosis, the evidence supporting the importance of physical factors is scanty. From a mechanistic point of view, the amount of menstrual fluid and the diameter of the uterine cavity outflow channels (i.e. the tubes and cervical canal) should play a role. It has been demonstrated in a primate model that retrograde menstruation is more frequent and more abundant in monkeys with endometriosis compared with those with a normal pelvis. Moreover, women with endometriosis menstruate more heavily than those without, and it has been observed that the pressure needed to overcome the intramural salpingeal resistance is lower in the former than the latter subjects. A study by Barbieri focuses the attention on the external cervical os. Some years ago his group developed a mathematical model to examine the factors that control the directionality of menstrual flow. Using an experimental uterine cavity, they observed that cervical os diameter was the single most important variable determining the percentage of fluid escaping through the artificial fallopian tubes. Now Barbieri reports an association between external cervical os stenosis of women with chronic pelvic pain and endometriosis. Diagnosis of stenosis was based on inability to fit a 4.5-mm cotton tip. A visual diagnosis of endometriosis was made at surgery in 24 of the 25 patients evaluated with the above characteristics. In a control group of 20 asymptomatic women no cervical os stenosis was observed. These intriguing findings should stimulate further research to determine the influence of anatomical variables in the development of the disease.

Barbieri RL. Stenosis of the external cervical os: an association with endometriosis in women with chronic pelvic pain. *Fertil Steril* 1998;70:571-3.

Barbieri RL, Callery M, Perez SE. Directionality of menstrual flow: cervical os diameter as a determinant of retrograde menstruation. *Fertil Steril* 1992;57:727-30.

## Pathogenesis: genetic factors

Molecular studies of cancer have demonstrated that tumor suppressor genes contribute to cell growth regulation. Genomic instability and DNA alterations are involved in progressive cell transformation. Somatic alterations of chromosome 17 or mutations in the *p53* tumor suppressor gene localized on it are frequently observed in premalignant and malignant genital cancers. Endometriosis is a benign condition, but aggressive and infiltrating behavior is sometime observed and association with endometrioid and clear-cell ovarian cancers have been repeatedly reported. Kosugi and co-workers used a 2-color fluorescence in situ hybridization method for analysis of endometriotic and normal archival tissue. Centromere-specific and locus-specific *p53* probes localized to chromosome 17 were selected to study 8 patients with severe endometriosis. Single cells localized to endometriotic lesions or normal endometrial glands were analyzed and identified as normal or abnormal based on fluorescence distribution in situ hybridization signals. Chromosome 17 aneuploidy was significantly greater in the endometriosis specimens (mean, 65%) than in normal endometrial cells (mean, 25%). No significant difference in the distribution of fluorescence in situ hybridization signals was observed among the 5 normal endometrial specimens. However, significant differences were found between the 8 endometriotic tissue specimens. In the authors' opinion, the increased heterogeneity of chromosome 17 aneuploidy found in endometriotic specimens supports a multistep pathway involving somatic genetic alterations in the development and progression of the disease.

Kosugi Y, Elias S, Malinak RL, Nagata J, Isaka K, Takayama M, Simpson JL, Bischoff FZ. Increased heterogeneity of chromosome 17 aneuploidy in endometriosis. *Am J Obstet Gynecol* 1999;180:792-7.

## Diagnosis

The possibility of diagnosing endometriosis without resorting to surgery is one of the key issue in modern management strategies. Transvaginal ultrasonography has been repeatedly demonstrated reliable in identifying endometriotic ovarian cysts and magnetic resonance imaging is being increasingly used to define the extension of deep, infiltrating lesions. However, none of the above techniques is of substantial help in determining the presence of superficial peritoneal or ovarian implants. This is a major clinical limitation because women with minimal or mild endometriosis, which essentially means superficial lesions, constitute the majority of the diseased population. Several studies addressed the performance of serum CA-125 measurements in the detection of endometriosis but the results, especially with regard to test sensitivity, are not consistent. Consequently, the systematic review and meta-analysis conducted by Mol et al. is very welcome because it throws light on an every day practical problem. The authors identified articles published in the scientific literature using MEDLINE and EMBASE. After exclusion of irrelevant titles and reports that did not allow construction of a 2 X 2 table or that dealt with patients with adnexal masses, 23 studies were included for analysis. There was no disagreement between the two investigators who evaluated study characteristics and results. The sensitivity of serum CA-125 measurement in the diagnosis of endometriosis varied between 0.04 and 1 and the specificity between 0.38 and 1. Due to quantitative heterogeneity between the studies, calculation of summary point estimates for sensitivity and

specificity were not meaningful. The diagnostic performance of CA-125 measurements was higher in case-control compared with cohort studies. The estimated summary ROC curve showed a low diagnostic performance when endometriosis at all stages was considered. Limiting the analysis to studies that included only subjects with stage III/IV disease increased the diagnostic capacity of the test to an acceptable level. For a specificity of 89%, the sensitivity was 47% (corresponding likelihood ratio of an increased CA-125 level = 4.3). An increase of the sensitivity to 60% resulted in a decrease of the specificity to 81% (corresponding likelihood ratio of an increased CA-125 level = 3.2). The authors conclude that, despite its limited diagnostic performance, routine use of serum CA-125 measurements in infertile women might be justified. However, it must be emphasized that the worst results were indeed observed in women with stage I/II disease, exactly those that are more difficult to identify with physical examination or other modalities. Accordingly, I wonder if CA-125 determination can still be considered an essential tool in the diagnostic work-up of a selected population which would probably be managed better with a symptom-oriented approach.

Mol BWJ, Bayram N, Lijmer JG, Wiegerinck MAHM, Bongers MY, van der Veen F, Bossuyt PMM. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998;70:1101-8.

# VII WORLD CONGRESS

## London, England



The next World Congress on Endometriosis will be held in London from the 14th to 17th May, 2000 in the Queen Elizabeth II Conference Centre which overlooks the Houses of Parliament and Westminster Abbey, right next to the Thames. London is one of the world's great cities and will be a spectacular place to visit in the first year of the next millennium.

Its convenience for travel from all major locations in the world and its central position for further travel in Europe makes it the ideal destination for both work and holiday.

We are planning a challenging scientific programme as well as an entertaining social one, culminating in a trip up the Thames to see the new Millennium Dome - Mr. Blair's great masterpiece!

We have decided to change the scientific programme for this congress and to focus it around those areas that we consider are of relevance to both clinicians and scientists.

The eight key symposia will be:

- Pain
- Damage  
(including adhesion formation)
- Recurrent and distant endometriosis
- New therapeutic agents
- Evidence-based medicine: infertility and endometriosis
- Frontiers in research
- Current controversies in endometriosis
- Debate: Surgical management of endometriosis

We aim to have three plenary lectures in each of these symposia, sponsored by the pharmaceutical industry through educational grants. They will, therefore, be completely secure for accreditation for Continuing Medical Education.

The general structure of the symposia is to start by describing the general physiological and basic sciences aspects of the title, next to relate those general issues to endometriosis specifically and finally, drawing those concepts through to medical and surgical management of the disease. In this way we hope to integrate all the issues, scientific and clinical, surrounding the key problems in endometriosis. The symposia are deliberately planned only to last an hour and a half to ensure that participants get clear, comprehensible conclusions without feeling overwhelmed.

There will be poster sessions and videos with prizes for the best in both.

Pre-congress workshops in Surgical Techniques, in Molecular Approaches to Endometriosis and patients and their support groups, are planned.

In summary, we are sure that the format of our programme, centered around the needs of the delegates, will be attractive, stimulating and educational.



# ON ENDOMETRIOSIS

May 14-17, 2000

## ● Social Programme

Alongside the academic programme we are arranging a lively social programme.

This will include an evening get-together on Sunday 14th May, and a formal opening ceremony on the morning of Monday 15th.

On Tuesday 16th, we plan a formal dinner at the Royal College of Obstetricians and Gynaecologists.

Finally, as we said before, we plan a full trip up the Thames from the Houses of Parliament, past the Tower of London to the Millennium Dome as the culmination of the congress.

Our conference organisers are also arranging a full programme of tours for both delegates and companions inside London and its nearby attractions including Hampton Court Palace and a Charles Dickens Walk.

All in all, London promises to be a stimulating and fascinating experience for everyone including clinicians, scientists, trainees, our industrial colleagues and patients and their supporters.

Join us in this most vital of cities at the turn of the millennium for what we know will prove to be an invigorating academic and social experience.



### Co-Chairmen:

Professor E.J. Thomas  
Chairman, Scientific Advisory  
Committee, RCOG

Professor R.W. Shaw  
President of the Royal College  
of Obstetricians and  
Gynaecologists

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## Medical treatment for infertility

Endometriosis is the most frequently encountered disorder at diagnostic laparoscopy for infertility. Mechanical distortion of tubo-ovarian anatomy, endometriotic cysts and diffuse periaxial adhesions may explain difficulty in conception at advanced disease stages. However, if and how minimal and mild endometriosis interferes with fertility has long been a matter of scientific debate. According to several experts, stage I and II disease is not the real cause of infertility and should be considered an incidental laparoscopic finding. If this is true, unexplained infertility and infertility associated with early endometriosis should be considered equivalent and have the same outcome in an assisted reproductive setting. There is still no consensus on the performance of several assisted reproductive techniques in women with endometriosis compared with other patient categories. Superovulation with IUI seems effective in the treatment of unexplained infertility. However, evidence supporting this approach in patients with minimal or mild endometriosis is still limited. Omland et al. conducted a prospective cohort study comparing 119 couples with unexplained infertility and 49 whose only anomaly was untreated stage I/II endometriosis at diagnostic laparoscopy, undergoing ovarian stimulation with AIH. No between-group difference was observed as to stimulation regimen, dose of gonadotropin, estradiol concentration, days of stimulation and number of follicles prior to insemination, and semen characteristics. The pregnancy rate was significantly higher for the unexplained infertility group, being 33.3% compared with 16.3% for the endometriosis group. Furthermore, an increased number of multiple gestations was obtained in the former group, resulting in a significantly higher implantation rate per cycle. The authors speculate that the observed difference reflects a difference in the etiology and pathogenesis of unexplained and endometriosis-associated infertility, and suggest that ovarian stimulation with IUI is indicated in the former situation, whereas in the latter the couples could be better off undergoing IVF-ET without undue delay.

Omland AK, Tanbo T, Dale PO, Abyholm T. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod 1998;13:2602-5.

## Surgical treatment

The findings of the multicenter Canadian trial have demonstrated that elimination of even a few ectopic endometrial implants increases the likelihood of pregnancy within the following 9 months. The difference with the untreated group was clinically and statistically significant and could influence treatment strategies in many couples with conception problems. Based on the study results, eight women need to be treated with laparoscopic ablation of minimal or mild endometriosis to achieve one more pregnancy carried beyond 20 weeks in comparison with no surgical ablation. However, the number needed to be treated in a unselected infertile population would be around 20, because minimal/mild endometriosis is found in no more than 40% of women undergoing laparoscopy for unexplained infertility. Furthermore, although a pathogenetic role of limited superficial implants in delaying conception seems probable, it is clear that physical elimination of visible foci does restore normal fecundity. The results of a recent Italian multicenter randomized trial contradict the finding of the ENDOCAN study, generating further perplexities. A total of 101 infertile women with laparoscopically diagnosed minimal or mild endometriosis were allocated to resection or ablation of visible lesions or no surgery, and were followed for 1 year. Five women withdrew from the study.

Twelve of 51 women (24%) in the resection/ablation group achieved a pregnancy compared with 13 of 45 (29%) in the no surgery group. Laparoscopic ablation of limited superficial endometriotic implants is simple, rapid, and safe. Although the treatment effect size in terms of postoperative conceptions is unclear at the moment, it seems sensible to eliminate visible lesions also in view of possible progression or pain symptom development. However, most of the available evidence suggests that fecundity of infertile women with untreated minimal or mild endometriosis is not significantly lower than that of women with unexplained infertility. If the above results are confirmed, the practical problem may not be eliminating or leaving visible foci untreated, but evaluating if it is worthwhile undergoing laparoscopy at all.

Marcoux S, Maheux R, Bérubé S and the Canadian Collaborative Group on Endometriosis. Laparoscopic surgery in infertile women with minimal or mild endometriosis N Engl J Med 1997; 337:217-22.

Gruppo Italiano per lo Studio dell'Endometriosi. Ablations of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Hum Reprod 1999;14:1332-4.



## World Endometriosis Society

- The first of it's kind

"While existing organizations struggle with how to adapt to the Internet, new associations have no restraints and are actually adapting faster."

- so says Roberta Speyer,  
publisher of OBGYN.net

Mrs. Speyer is referring to the fact that the World Endometriosis Society has decided to retain her company to handle all registrations and membership applications through their web site at:

<http://worldendo.obgyn.net/>

This service, to be implemented over the summer, will allow registrants of future WES congresses to select their program track on-line, make payment, and receive a printed confirmation and program via e-mail. Payment of Society dues and application for membership to the Society will be facilitated to allow the Society to keep the high cost of paper, printing and mailing from devouring the budget, as it does for most young societies.

For you cyber minded WES members, check out these URLs:

<http://worldendo.obgyn.net/>  
<http://www.obgyn.net/endo/endo.htm>  
<http://www.endozone.org/>  
<http://www.obgyn.net/>

## Surgical treatment for stage III/IV disease

The pathogenesis of ovarian endometriotic cysts is controversial. An endometrioma may be the result of either metaplasia of the coelomic epithelium covering the ovary or inversion and progressive invagination of the ovarian cortex after adhesion to the pelvic peritoneum caused by local implantation of endometrium regurgitated through the tubes. Many experts agree that endometriomas are pseudocysts and that what we identify as a capsule is actually inverted ovarian cortex. Accordingly, radical removal of these lesions would be unnecessary and reduce the ovarian reserve. Other surgeons maintain that simply opening the endometrioma and treating its surface would increase the risk of recurrence. Given the above scenario, the two recent studies on the topic published recently in *Fertility and Sterility* are timely and interesting.

Hemmings et al. operated 156 women with ovarian endometriomas of  $\pm 3$  cm in diameter, performing laparoscopic ovarian fenestration of at least 2 cm followed by bipolar electrocoagulation of the inner wall in 80 cases, laparoscopic ovarian cystectomy in 23, and microsurgical ovarian cystectomy

at laparotomy in 53. The 36-month cumulative probability of conception in women who underwent fenestration and coagulation was higher (60%) compared with the other two surgical modalities (slightly over 40%), although not significantly so. However, time to pregnancy was significantly different, as the mean  $\pm$  SD number of years to conception was  $1.4 \pm 0.2$  after fenestration,  $2.2 \pm 0.5$  after laparoscopic cystectomy, and  $2.4 \pm 0.5$  after microsurgery at laparotomy. The 36-month cumulative recurrence rate was similar, being respectively 12%, 8%, and 9%.

Beretta et al. randomly allocated 32 patients to laparoscopic cystectomy and 32 to endometrioma drainage with bipolar electrocoagulation of the inner lining. The 24-month cumulative recurrence rates of dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain were lower in the former than the latter group being, respectively, 16% vs 53%, 20% vs 75%, and 10 vs 53%. The median interval between the operation and the recurrence of moderate to severe pelvic pain was 19 months in the cystectomy group and 9.5 in the

coagulation group. Also the 24-month cumulative pregnancy rate was significantly different, being 66.7% in the former and 23.5% in the latter group.

The opposite findings of the above studies obviously do not disentangle the issue and leave us with unsolved surgical uncertainties. However, the quality of the evidence presented could be different, as only formal prospective, randomized clinical trials may limit confounding and biases.

Hemmings R, Bissonnette F, Bouzayen R. Results of laparoscopic treatments of ovarian endometriomas: laparoscopic ovarian fenestration and coagulation. *Fertil Steril* 1998; 70:527-9.

Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril* 1998;70:1176-80.

## Goes Digital

"Our membership is distributed around the world. The Internet and e-mail are the only logical solution to our member's information needs"

- says *Professor Rodolphe Maheux, Executive Secretary of WES.*

"We will be the crucible that Mrs. Speyer and OBGYN.net can use to test the concept of a virtual society in. What will work for our Society will also work for other societies. We have a long history of mutual collaboration with OBGYN.net and are pleased to be the first Society to offer these advantages to our members. Who knows where it will all end up but live Internet broadcasts from WCE 2000 sessions are a definite possibility."

## Pathogenesis of pain

The pathogenesis of pain in women with endometriosis is far from clear and it has been demonstrated that there is no consistent correlation between disease stage and frequency and severity of various pain types. Moreover, patients with similar lesions and anatomical distortions may have completely different symptomatologic patterns. It has been postulated that adhesions may have a role in determining at least part of pain symptomatology, but the evidence in this regard is limited. Tulandi and co-workers evaluated the presence of nerve fibers and different histopathological aspects of adhesions excised laparoscopically in 50 women, 17 of whom had pelvic infections, 10 previous surgery, and 19 endometriosis. Nerve fibers were identified by immunocytochemistry staining with an antibody to neurofilament in 39 of the 50

subjects studied. However, there was no significant difference in the proportion of specimens with nerve fibers and in the mean nerve score in adhesions due to previous infection, surgery, or endometriosis. More importantly, no difference was found in the amount of nerve fibers and the mean nerve score in adhesions from women with or without pelvic pain. The authors conclude that presence of nerve fibers in abdominopelvic adhesions is a common finding not related to the underlying disease or pelvic pain.

Tulandi T, Chen MF, Al-Took S, Watkin K. A study of nerve fibers and histopathology of postsurgical, postinfectious, and endometriosis-related adhesions. *Obstet Gynecol* 1998;92:766-8.



## Call for bids to host the Xth World Congress - 2006

The World Endometriosis Society will be entertaining offers to host the Xth World Congress on Endometriosis. Judging from the past success of congresses, as well as aid from the newly formed Society, the opportunity to host such an event will allow local organizers an outstanding international forum to showcase in an outstanding international forum.

### Requirements for a host city bid:

- The congress president should be a PhD or MD residing in the country where the congress will be held and be a regular member of The World Endometriosis Society. The President should assume the responsibility for the organization of the congress and should be supported by a Local Organizing Committee and the International Scientific Committee of WES.
- None of the participants coming from various countries should have problems obtaining a visa to the congress.
- All financial risk is taken by the organizers of the congress.
- A budget must be submitted with the application. This will have to be approved by the WES council. Note: the total number of participants to the VI World Congress on Endometriosis in Québec City was 825.
- Provision should be made within the budget for Council members and past presidents of WES to have travel funds, registration and accommodation enabling their participation in the Congress.
- Organizers are encouraged to publish proceedings of the congress.
- The congress must have a separate fee structure for members and non-members of WES and must include a provision in the budget to remit 20 percent of registration fees to WES. This has already been agreed with the WES Congress scheduled for the Netherlands in 2004.
- The President will be required to sign an official agreement with WES.
- WES has a web site and can include Congress information.
- WES has a Newsletter and will include information on the Congress.
- WES can provide the expertise of a Professional Congress Organizer to assist in selecting local companies.
- For further information, please direct your inquiries to the WES Central Business Office.

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## Future Venues

|                           |                             |
|---------------------------|-----------------------------|
| May 14-17, 2000.....      | London, UK                  |
| February 22-27, 2002..... | San Diego, USA              |
| September, 2004.....      | Maastricht, The Netherlands |
| 2006.....                 | To be determined            |