Getting to know endometriosis

Awareness. This is what it is all about. And it has to happen on so many different levels before we can truly say that we know endometriosis.

This month national support organisations across the world staged events as part of Endometriosis Awareness Month to increase knowledge about endometriosis. This is an annual initiative, where volunteers come out in force to make sure the general public gets to know endometriosis through rallies in parks, informational seminars, parliamentarian briefings, TV and radio appearances, poster campaigns, and fundraising balls. I applaud these efforts and encourage everyone to get involved and support these initiatives in our respective countries. We need to ensure that everybody knows about endometriosis!

The Society’s efforts to “get to know endometriosis” are through this e-Journal and at the World Congresses. It is a core part of our mission to “promote the exchange of information”.

The 10th World Congress on Endometriosis (WCE 2008) is now exactly one year away, and on page 13 you can read David Healy’s highlights from the congress programme. It will be a “state of the art” congress, which you will not want to miss out on, if you are in this field. Register now – and let’s meet in Melbourne to get to know endometriosis better!

There is a third level, however, which we mustn’t forget when it comes to knowledge and awareness, and this is with our governments.

A strategic alliance between physicians and patients in Europe has resulted in unprecedented recognition of endometriosis by the European Parliament in 2005 and 2006. These groups have taken this recognition one step further and an informational seminar for Members of the European Parliament took place on 28 March to increase their knowledge of endometriosis and its impact.

The Society’s Secretary General spoke at the seminar, and reminded those present that it is time we see investment into female benign chronic diseases so that treatments can be developed, which will preserve these women’s fertility, improve their quality of life, and reduce socio-economic costs. I agree that by taking care of women, we are safeguarding our future! See page 6 for more details about the day when clinicians, scientists, women with endometriosis and legislators came together to call for investment into causal research.

And – speaking of research – it is now possible for you to make a donation to the World Endometriosis Research Foundation when you renew your WES membership. If we pool our efforts it will benefit us all. Read more on page 2.

Finally I would like to welcome Professor Liselotte Mettler from Kiel University in Germany to the WES Council. Professor Mettler is replacing Dr Agneta Bergqvist, who stepped down last year, and she brings a lot of experience with endometriosis to our Society.

May 2007 be a good year for you; and, may 2007 be the year where more people get to know endometriosis!

Sincerely,

Rodolphe Maheux
EDITOR’s MESSAGE

Dear readers,

This is a particularly interesting and enriching issue of the e-Journal, which tackles two major clinical topics as well as a relevant theme: the environment and its major impact on reproductive health.

In our guest editorial, Drs Karen Ballard and Jeremy Wright present an timely opinion paper on the serious issue of diagnostic delay in endometriosis. The absence of a diagnosis can be physically and emotionally detrimental for a woman, and thus addressing factors for this delay, such as increasing awareness and education, undoubtedly deserves more attention. This definitely meets up one of our Society’s objectives!

The second major clinical topic is adhesions in endometriosis. Drs Anthony Imudia and Michael Diamond provide a highly relevant review of this subject where “…more than 70% of women with endometriosis have adhesions, which are likely to contribute to endometriosis symptoms.” Yet “…choosing surgery to diagnose and treat the pelvic adhesions related to the disease process can be associated with even greater adhesion formation.” This article elegantly reviews the mechanisms behind adhesion formation, classification, the variability in adhesions, possible pathogenesis mechanisms, and clinical consequences.

The last and not the least issue addressed in this volume is the environment. We thank Professor Linda Giudice from the University of California and Founder of the Program on Reproductive Health and the Environment for sharing with our readers the key messages from “The Summit on Environmental Challenges to Reproductive Health and Fertility”, which was held at the University of California in January this year. This is a timely update as we all know the potential impact of environmental contaminants on endometriosis.

Finally, do not miss the update on WCE 2008 and programme highlights from Dr David Healy, President of WCE 2008, and seize the wonderful opportunity to take part in the congress!

You are kindly invited to react to these articles or to any other issue that may stimulate a constructive exchange of information.

Sincerely,

Ali Akoum

NEWS ROUND UP

Professor Liselotte Mettler joins WES Council
Professor Mettler is well known in endometriosis as well as one of the early pioneers in endoscopic surgery. She is professor of obstetrics and gynaecology at Kiel University, and head of the Kiel School of Gynaecological Endoscopy and Human Reproduction. During her career she has contributed to the literature with more than 600 publications and seven books.

We are delighted to have Professor Mettler’s expertise on the Council and are looking forward to a fruitful collaboration! Welcome!

World Endometriosis Research Foundation
The Foundation is a joint initiative between the WES, ESHRE and the ASRM, and has been established as an international platform to foster research in endometriosis, and to ensure this is not carried out in isolation. Sharing data, building on results and facilitating international multi-centre clinical trials may herald a new era of meaningful research in endometriosis. To donate to endometriosis research:
http://www.endometriosisfoundation.org

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As far back as 1918, in his book Fibroids and Allied Tumours, Cuthbert Lockyer eloquently described the nature of pelvic pain and its relationship to endometriosis. In addition to his own accurate vignettes of women presenting with rectovaginal endometriosis, he drew on the published experience of Cullen who detailed the symptomatology of pelvic pain, dyschesia and dyspareunia.

Sampson, in his predominantly pathophysiological descriptions of the disease emphasised the presence of menorrhagia, probably to support his theory of retrograde menstruation, which he demonstrated by operating on women during their menstrual periods. Despite the classical symptoms of the disease being reported in all the major text books over the years, clinicians are often not alerted to the symptoms of dysmenorrhoea, backache, dyspareunia and dyschezia and the associated signs of pelvic tenderness, particularly tenderness in the posterior pelvic cul-de-sac that give rise to a possible diagnosis of endometriosis.

An ongoing debate over the aetiology and pathogenesis of endometriosis suggests that there are three different classifications of endometriosis although more recently, it has been argued that there are two predominant types; Cullen’s disease, which is infiltrating, and Sampson’s disease, which is superficial. This distinction is, however, not clear cut, as superficial disease can be present in women with deep disease, and ovarian endometriomas can be present in both disease groups. Despite this growing awareness of symptom patterns relating to endometriosis, women continue to experience a diagnostic delay of around eight years.

In this editorial, we consider the different methods of diagnosing endometriosis, the reasons leading to a diagnostic delay, and the impact that this can have on women and their families. We conclude with some suggestions for reducing the delays in diagnosis.

Making the diagnosis of endometriosis

Diagnosing endometriosis can be difficult unless one is aware of the complex symptom patterns, their protean nature and the absence of clear physical signs or specific diagnostic tests. There is considerable symptom overlap with other conditions such as irritable bowel syndrome and chronic pelvic inflammatory disease. Indeed, in a recent retrospective study of medical records, 19% of women with a diagnosis of endometriosis were also given a diagnosis of irritable bowel syndrome. Similar findings are reported in a retrospective study of women with chronic pelvic pain.

A definitive diagnosis of endometriosis can only be made at surgery, with histological confirmation of both typical and atypical lesions. Redwine, in a cohort study of 137 consecutive women undergoing laparoscopy and multiple biopsies of suspect endometriosis, has demonstrated that atypical lesions, particularly white lesions, appear more frequently than typical black and red lesions and are easily missed.

The need for histologic confirmation continues to be a matter of debate. There is some evidence from diagnostic studies, as well as a systematic review, to support the need for histological confirmation of a visual surgical diagnosis of endometriosis. A particular problem with these studies, however, is that a normal laparoscopy is dependent on the observer and may have no independent confirmation.

Despite the caveats stated above, surgical diagnosis of endometriosis is regarded as the ‘Gold standard’ but it is not without risks, with a large multi-centre study reporting a complication rate of 2.4 per 1000 cases. In addition, there are personal and institutional financial consequences attached to any surgery, as well as the potential anxiety for women undergoing the procedure. This is particularly pertinent since it has been shown that around half of the women undergoing a diagnostic laparoscopy for chronic pelvic pain are diagnosed with a ‘normal pelvis’. Hence, there have been, and continue to be, attempts to produce a non-surgical diagnostic tool to aid the diagnosis of endometriosis.

To date, non-surgical approaches to diagnosing endometriosis have largely focused on the use of imaging techniques, and in particular transvaginal sonography (TVS). Whilst there is good evidence, reported in a systematic review, to support the use of TVS for the diagnosis of endometrioma, it has been shown to be less accurate in diagnosing pelvic endometriosis and in excluding deep endometriotic deposits. There are, however, few reliable prospective diagnostic studies in this area, the reported studies being opportunistic scanning of women with a strong clinical suspicion of endometriosis, and further research would be of benefit.

There is limited evidence to support the use of Magnetic Resonance Imaging (MRI) in the diagnosis of pelvic endometriosis, although small studies report a positive predictive value of 86% and a negative predictive value of 46%, with slightly better results being achieved with fat-suppressed images compared with conventional images. As imaging techniques improve and more is known about linear array scanners, with greater resolution it may be possible to both diagnose and stage endometriosis with more accuracy.

Can the delays in diagnosing endometriosis be reduced?

Karen D Ballard & Jeremy T Wright

Women’s Health Research Unit, Postgraduate Medical School, University of Surrey, Guildford, Surrey, UK

As imaging techniques improve and more is known about linear array scanners, with greater resolution it may be possible to both diagnose and stage endometriosis with more accuracy.
TVS, in conjunction with other soft markers such as medical history, symptom reports and pelvic examination, has been used in an attempt to develop a non-surgical diagnostic tool for endometriosis. Whilst this study confirmed that ovarian endometriosis could be reliably diagnosed with high resolution ultrasound in combination with clinical examination; in this sample of women predominantly presenting with infertility, other reliable soft markers of endometriosis elsewhere in the pelvis could not be identified. Location of pelvic pain may help to identify specific sites of endometriosis. Indeed, in a prospective study of women with chronic pelvic pain, location and intensity of self-reported pain was found to be predictive of posterior cul de sac deep infiltrating endometriosis.

Serum biomarkers such as CA-125 and CA-19-9 have also been considered as potential diagnostic measures for endometriosis. In a systematic review and meta-analysis, however, CA-125 was found to be of limited value in detecting endometriosis, although it performed slightly better in the detection of severe disease, probably due to its ability to detect ovarian endometriomas. As shown by Redwine, endometriomas are a marker for deep infiltrating endometriosis elsewhere in the pelvis. It has been suggested that CA-19-9 may be a more accurate biomarker, although there is limited evidence for this. Other serum markers such as cytokine interleukin-6 and leptin have been investigated, but so far, the evidence to support their predictive value is limited. It has been suggested that it may be necessary to use multiple biomarkers to improve the diagnostic accuracy.

Over the past few years, there has been much debate about the empirical use of either the combined oral contraceptive pill or GnRH analogues to reduce symptoms in the diagnosis of endometriosis. In their guidelines on the management of chronic pelvic pain, both the American and the Royal College of Obstetricians and Gynaecologists recommend this approach prior to a diagnostic laparoscopy; although very recently the RCOG guidelines on the management of endometriosis suggests that this should be only “if a woman wants pain symptoms suggestive of endometriosis to be treated without a definitive diagnosis.” The empirical use of GnRH in this way is also supported by others including consensus from 52 practising gynaecologists.

It would appear, however, that this approach to diagnosis is based on the findings from one small multi-centre randomised control trial of 100 women, half of whom received depot leuprolide and the other receiving placebo. Whilst this study, with all its biases, does confirm that depot leuprolide reduces pelvic pain, further analysis does not support the empirical use of depot leuprolide as a diagnostic tool. Using the figures that the authors quote in the paper and plotting them on a 2X2 table, pain relief following depot leuprolide as a diagnostic test has a sensitivity of 82% (95% CI 69-95), a specificity of 27% (95% CI 1-54), a positive likelihood ratio of 1.13 (95% CI 0.76-1.67) and a negative likelihood ratio of 0.67 (95% CI 0.20-2.23). In effect, this means that it is a very poor test for determining the presence of endometriosis, although slightly better at determining the absence of endometriosis. In practice, this means that based on a 30% prevalence of endometriosis in women with chronic pelvic pain, a trial of depot leuprolide resulting in pain relief will increase the probability of a woman having endometriosis from just 30% to 33%. If the woman does not experience pain relief, however, we can say that her chances of having endometriosis are reduced from 30% to 22%.

In other words, the response to treatment with depot leuprolide adds very little to our knowledge of her chances of having endometriosis based on symptoms alone. The advice from these colleges should be treated with some caution and women opting for this treatment strategy should be made aware of the evidence.

The impact of delayed diagnosis

The complexity surrounding the diagnosis of endometriosis has contributed to a significant delay in diagnosis, with studies showing an average delay of 11.7 years in the US compared with an 8-year delay in UK and 6.7 years delay in Norway. In a recent study of women’s experiences of endometriosis, 4 key factors leading to a delayed diagnosis were identified:

1. symptoms were normalised by women leading to a delay in seeking medical help;
2. symptoms were normalised by family doctors leading to a delay in referral to a specialist;
3. symptoms were treated with hormonal therapy, leading to some relief of symptoms prior to a diagnosis being made; and
4. non-discriminatory investigations, providing false negative results were used.

Whilst there do not appear to be any other studies focusing on the factors leading to a delayed diagnosis of endometriosis, this and other studies have shown the absence of a diagnosis to be physically and emotionally detrimental, with women expressing concerns that their pain might be due to other more sinister causes such as cancer. Moreover, these studies also demonstrate that women obtained enormous emotional relief from medical encounters where their pain is taken seriously and where something is being done to find the cause of their pain.

A further consideration surrounds the notion of endometriosis as a progressive disease, with increasing pelvic inflammatory reaction, adhesion formation and expansion of ovarian endometriomas. If this is the case, early diagnosis of endometriosis could lead to medical interventions such as suppression of menstruation, which may delay the onset of severe symptoms and help protect fertility.

The delays in diagnosis: can they be improved?

Since the available data show that teenage girls’ reluctance to seek medical help for their pelvic pain arises from their belief that their symptoms are ‘normal’, the first step in reducing the diagnostic delay is to increase awareness amongst this age group of abnormal and normal menstrual experiences.
Menstrual pain requiring time away from school should not be perceived as normal and should trigger appropriate referral and advice. School medical services play a vital role in bringing about this change. Awareness of the symptoms relating to endometriosis and sensitivity in eliciting these symptoms needs to increase amongst family doctors, who play an important part in both the diagnosis of endometriosis as well as referral for specialist diagnosis, treatment and continuing care. Dissemination of research findings and review papers in more general journals, as well as discussion and clinical update seminars are invaluable. The diagnosis and management of chronic pelvic pain should feature in the undergraduate and post-graduate curriculum and clinical algorithms should be developed to aid speedy diagnosis. With the current lack of accurate non-surgical diagnostic tests for endometriosis, we suggest that women continue to need a diagnostic laparoscopy and histological biopsy to confirm the presence or absence of disease. It is important, however, to recognise that even this is not 100% accurate, although its precision may well be enhanced in the hands of endoscopic specialists skilled in the recognition of endometriotic deposits. Understanding the risks associated with diagnostic laparoscopy, including the possibility that a diagnosis will not be made means that women need to be counselled properly prior to consenting to the procedure and also be informed about the extent to which the procedure is primarily diagnostic or offers treatment at the same time.

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Stakeholders in endometriosis come together in the European Parliament

Legislators, physicians and women with endometriosis from across Europe came together in the European Parliament on 28 March to call for more investment into causal research in endometriosis. The core theme of the seminar was the lack of prioritisation of women's health when it comes to investment in research for benign, chronic diseases.

The seminar was hosted by the vice-president of the European Parliament, Diana Wallis MEP, who was also the lead author of the 2005 Written Declaration on Endometriosis, which attracted more signatures by MEPs than any other human health issue. Yet investment in causal research is still lacking behind.

The chair of the ESHRE SIG on Endometriosis, Professor Thomas D’Hooghe said: “If we as clinicians and scientists are truly to help women get optimal treatment, significant investment is needed into causal research, so that we can work towards prevention of endometriosis for the next generation of women. At a time where gender equality appears to be a priority, women’s health and endometriosis in particular is being neglected despite its prevalence and impact on society.”

These challenges have been formally acknowledged by the Italian Senate, the first EU member state to recognise endometriosis as a social disease. The Senate’s 12th Commission on Hygiene and Health is embarking on a five year plan to address: treatment by specialists within multi-disciplinary networks of excellence; information campaigns to reduce time to diagnosis; reimbursement; national registries to monitor epidemiology and efficacy of treatments; support; disability allowance; and investment in research.

For more information, please see: www.endometriosis.org/european_parliament.html
**Introduction**

Endometriosis, whose aetiology is polygenic in nature, has different forms of clinical presentation and surgical findings. One of the most common surgical finding in women with endometriosis is adhesive lesions in different parts of the pelvis and abdomen, with variable physical and histological characteristics.

It is estimated that more than 70% of women with endometriosis have adhesions. These adhesions are often likely to contribute to the clinical symptoms and problems like chronic pelvic pain, infertility, dysmenorrhea, dyspareunia and dyschezia commonly seen in these patients, as well as bowel obstruction. However, some women with endometriosis have no adhesions identified during laparoscopy.

There are a few hypotheses to explain this variable clinical presentation; these include the pathophysiology of endometriosis, patient's medical history and the type of endometriotic lesion (colour, size and characteristics). In patients that develop adhesions, other key questions include the location of the adhesive/endometriotic lesions, and their clinical consequences in these women? These are some of the questions we intend to address with this article review.

**Adhesion**

Adhesions can simply be defined as connections between tissues at two sites that are normally separate. They often appear as thin sheets of tissue or as thick fibrous bands which may contain nerves and vessels.

These tissues develop as a result of our body repair mechanisms response to tissue injuries resulting from surgery, inflammation, infection, trauma, or even the placement of foreign substance in a particular location of the body.

The mechanisms behind adhesion development in different locations throughout the human body are likely very similar, with very little variation. Whenever there is an injury to a tissue, healing pathways are activated provoking the interaction of a complex cascade of cellular events that generates resurfacing, reconstitution, and restoration of the normal anatomy of the injured tissue, with the teleologic intention of correcting the original insult.

Postoperative development of adhesions can be classified as de novo or reformed. De novo adhesions are the abnormal fibrous connections at sites that did not have adhesions initially, whereas reformed adhesions develop at sites of previous adhesiolysis. Further sub classification of each type is based on whether additional surgical procedures (other than adhesiolysis) were previously performed at the site at which they are located (Table 1).

Adhesions are observed in more than 70% of women with endometriosis, with or without the history of previous surgery. According to Parker et al., 74% of the women enrolled in their studies had pelvic adhesions at the time of the first study surgery, while 82% had adhesions at the second study surgery. These rates are very similar to the approximately 75% - 85% of women without prior history of endometriosis surgery who were noted to have pelvic adhesion at an initial surgery².

<table>
<thead>
<tr>
<th>Type 1</th>
<th>De novo adhesion formation; development of adhesions at sites that did not have adhesion initially</th>
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<tr>
<td></td>
<td>A: No operative procedure at site of adhesion formation</td>
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<tr>
<td></td>
<td>B: Operative procedure performed at site of adhesion formation</td>
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<table>
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<tr>
<th>Type 2</th>
<th>Adhesion reformation; redevelopment of adhesions at sites at which adhesiolysis was performed</th>
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<tbody>
<tr>
<td></td>
<td>A: No operative procedure other than adhesiolysis at site of adhesion reformation</td>
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<tr>
<td></td>
<td>B: Operative procedure performed in addition to adhesiolysis at site of adhesion reformation</td>
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Table 1. Classification of Postoperative Adhesion Development
Variability in adhesion formation in women with endometriosis

One key question is why about 30% of women with endometriosis have no evidence of adhesions in the pelvis or abdomen? In part this may be explained by analysing some of the postulated pathogenesis mechanism as the possible causes of endometriosis, and the characteristics of the endometriotic lesions. Potentially, the degree of involvement of these different mechanisms giving rise to endometriosis in a particular individual will determine the clinical manifestation and extent of the adhesion development.

1. Intensity of retrograde menstruation:
Retrograde menstruation may play a pathophysiologic role in the development of endometriosis. Any anatomic alterations of the pelvis that increase tubal reflux of menstrual endometrial cells should increase a woman's chance of developing endometriosis. Evidence supporting this hypothesis is derived from the observation that the incidence of endometriosis is increased in young females with genital tract obstructions that prevent passage of menses into the vagina, and therefore increase the likelihood of tubal reflux.

The origin of endometriosis is not only dependent on alteration of pelvic anatomy but on the intensity of retrograde menstrual flow and an individual's body's response to these ectopic endometrial cells in the pelvis. Therefore, the development of endometriosis, and possible adhesions around the implant, must be related to additional factors, like the amount and intensity of endometrial tissue reaching the peritoneal cavity or the capacity of a woman's immune system to eliminate refluxed menstrual debris.

2. Degree of immunological changes:
As mentioned earlier, most women with retrograde menstrual flow do not develop endometriosis; this is why multiple investigators suggested a direct relationship of this variability in response to immunological changes.

A summary of some of the evidence for altered humoral and cell-mediated immunity in the pathogenesis of endometriosis are that in women with endometriosis:

a) Natural killer cell activity may be reduced, resulting in decreased cytotoxicity to autologous endometrium.

b) Deficient cellular immunity may result in an inability to recognise the presence of endometrial tissue in abnormal locations.

c) An increased concentration of leukocytes and macrophages in the peritoneal cavity and ectopic endometrium. These cells secrete cytokines (eg, interleukin-1, 6, and 8; tumour necrosis factors, RANTES) and growth factors into the peritoneal fluid of women with endometriosis.

d) Increased secretion of various cytokines by endometriotic implants and inflammatory cells into the peritoneal cavity leads to proliferation of implants, recruitment of capillaries (eg, by vascular endothelial growth factor), and chemotraction of leukocytes to these foci of peritoneal inflammation.

e) Other molecular biology changes including:
1) Decreased apoptosis
2) Increased integrins
3) Increased mismatch repair activities.

The immune system may play a role in determining who will develop endometriosis, as well as the extent and clinical manifestation of the disease. In women who go on to develop endometriosis and possibly adhesions, the endometrial cells escape being cleared by the immune/inflammatory response because of any of the above changes in the immune system which enable the endometrial fragments to attach to peritoneal mesothelial cells, and then invade into the submesothelial extracellular matrix, where they can potentially persist and proliferate into macroscopic disease.

3. Genetic predisposition:
Genetic factors probably influence an individual's susceptibility to endometriosis. The possibility of a familial tendency for endometriosis has been recognised for several decades.

If a woman has endometriosis, a first-degree relative has a 7 percent likelihood of developing the disorder as compared with 1 percent in unrelated persons. Concordance in twins has also been observed. Further studies are needed to identify major susceptibility gene(s) involved in pathogenesis. Multiple genes which may interact with each other and the environment to confer disease susceptibility and produce the phenotype have been proposed. The expression of this genetic liability may depend on an interaction with environmental factors. Although more studies are needed to confirm the exact role of genetics in the pathogenesis of endometriosis, it would be understandable that individuals with higher genetic predisposition could have a more florid clinical manifestation of the disease, and hence could have findings that are not seen in other patients without the same genetic predisposition.

4. Propensity for oxidative stress (free radicals):
Reactive oxygen species created through oxidative stress may be another component of the inflammatory reaction involved in endometriosis and adhesion formation. The inflammatory process is thought to be a fundamental triggering factor for endometriosis. Free radical metabolism has been shown to be closely related to the inflammatory process and the development of complications of endometriosis like adhesions. Peritoneal fluid volume in women with endometriosis is increased, and the content significantly differs from women without endometriosis.
The number of macrophages is greater, and demonstrate increased phagocytosis, and increased secretion of cytokines, prostaglandins, growth factors, and enzymes. Consistently, iNOS activity and NO production from the peritoneal macrophages were significantly increased in endometriosis. Moreover, it has been shown that peritoneal fluid nitrite and nitrate content is higher in the menstrual cycle. Stimulatory agents like interferon-alpha and interferon-gamma with lipopolysaccharide (LPS) can activate macrophages in the endometriotic peritoneal fluid to increase iNOS and NO production, but not in normal women. There is an increase in oxidatively modified lipid–protein complexes, which are both strong chemotaxins for monocytes and inducers of cytokine secretion in peritoneal fluid of women with endometriosis. Additionally, defensive enzymes against oxidative stress in the endometrium of women with endometriosis show altered expression patterns.

There is exaggerated expression of manganese and copper/zinc superoxide dismutase in the endometrium of women with endometriosis and adenomyosis throughout the menstrual cycle. The role free radicals play in the inflammatory process leading to adhesion formation is very similar to that of endometriosis; this may be why many of the women with this disease will have adhesions, based on the degree of free radical production and availability of scavenger molecules. It has been postulated that reactive oxygen species are involved in adhesion development following surgery. Free radicals are likely to be produced locally in peritoneal tissue during laparoscopy as a result of tissue hypoxia and the ischemia/reperfusion process. While it has been suggested that free radical production may be related to exposure to hyperoxic environment (room air) during laparotomy, we have demonstrated increased production of reactive oxygen species in fibroblast cell culture under hypoxic conditions.

5. Patient’s past medical history:
The presence or absence of adhesions in a patient with endometriosis also depends on her past medical history. A patient may have pelvic adhesions because of her prior history of pelvic inflammatory disease and not necessarily from her endometriosis. Also patients with a past surgical history either for endometriosis or other medical problem can have adhesions secondary to their prior surgery. As noted earlier, there is a high rate of de novo adhesion formation and reformation in women with chronic pelvic pain due to endometriosis after a surgery specifically intended to treat both adhesions and endometriotic lesions.

6. Characteristics of endometriosis/adhesive lesion:
Many investigators have tried to describe the characteristics of endometriotic lesions or adhesions on the basis of colour, size and consistency (thin or thick). Stratton et al. grouped the different possible endometriotic lesions as black, red, white, mixed colour or endometriomas. They studied which type of lesions is more likely to have histological confirmation of endometriosis and found that white lesions, mixed colour lesions, endometriomas, and larger lesions by depth and width were more likely to be endometriosis when compared with smaller, black or red lesions.

Most lesions seen are black or red and more visible during surgery but, in their hands they correlated poorly to the true existence of endometriosis. diZerega et al. correlated the likelihood of adhesion formation with the colour of endometriotic lesions, and identified that more adhesion development is seen in women with red colour endometrial implants. Additionally, it has been seen consistently that the bigger the size of the lesion, the more likely the presence of adhesions, which correlates directly with the type and severity of symptoms seen in various patients.

None the less, some women with severe endometriosis can be asymptomatic, while others with minimal lesions can have severe symptoms. Ovarian endometriomas are adherent to the surrounding pelvic structures in more than 90% of cases. Parker et al. found that adhesion consistency has a significant impact on the likelihood of adhesion reformation, highly consistent (thick) adhesions are more likely to reform than thinner adhesions. However, it is uncertain whether this relates to the characteristics of the adhesions per se, or other factors such as the exposed raw surface area after lysis or excision of adhesions. This concept also stands true for the size of endometriomas, which are more associated with adhesion formation and high recurrence rate.

Location of endometriotic lesions and adhesions
While endometriotic implants have been seen in different parts of the body, the majority of the time they are located in the vicinity of pelvic structures. The most common sites of endometriosis, in decreasing order of frequency, are:

- the ovaries;
- anterior and posterior cul-de-sac;
- posterior broad ligaments;
- uterosacral ligaments;
- uterus;
- fallopian tubes;
- sigmoid colon; and
- the appendix and round ligaments.

The location of endometriosis and adhesions are important, as is how much these changes have altered the anatomy of the affected structure, which will likely relate to the clinical presentation. In fact, many people with endometriosis will go unnoticed because the extent of the lesions is not enough to produce any clinically recognisable symptoms.

In contrast, there is an association between severe dysmenorrhoea and extent of pelvic adhesions located in the pouch of Douglas.
Clinical Consequences

Matching of patients with endometriosis and possible adhesions with the right treatment approach can prove difficult to clinicians.

This is so because choosing surgery to diagnose and treat the pelvic adhesions related to the disease process can be associated with even greater adhesion development as part of the post-surgical healing process.

The usual symptoms of endometriosis are pelvic pain (which may be chronic but is often more severe during menses or at ovulation), dysmenorrhea, deep dyspareunia, cyclical bowel or bladder symptoms, abnormal menstrual bleeding, infertility, and chronic fatigue. However, these symptoms are also present in other gynecologic disorders (pelvic inflammatory disease) or irritable bowel syndrome, which often results in diagnostic delay. On the other hand, many women with endometriosis are completely asymptomatic.

The stage of endometriosis is not necessarily correlated with the presence or severity of symptoms. This paradox may be explained by the hypothesis that symptoms are more related to a local peritoneal inflammatory reaction than the volume of the implants.

But, pelvic pain may be more common in women with deep, infiltrating implants. In particular, severe dyspareunia and painful defecation during menses are suggestive of posterior deep infiltrating disease. Often, the depth of infiltration correlates with the type and severity of symptoms.

The overall pregnancy rate in patients with endometriosis and adhesions together, versus with endometriosis alone, has been reported to be not different; the only difference is that patients with endometriosis alone tend to conceive faster than patients with endometriosis and adhesions.

Conclusion

Endometriosis is a complex medical problem with variable clinical presentations.

The extent and association of adhesion with endometriosis is likely determined by factors like the intensity of retrograde menstruation, immunologic changes, genetic predisposition, extent of oxidative stress, and the patient’s past medical history.

Surgical cases intended to treat endometriosis is associated with a high rate of postoperative adhesion reformation and therefore should be considered when determining a clinical treatment plan.

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CONGRESS SCENE

Highlights from the 2007 UCSF-CHE Summit on Environmental Challenges to Reproductive Health and Fertility
28-30 January 2007, San Francisco, USA

Professor Linda Giudice, Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences; Founder, Program on Reproductive Health and the Environment; Summit 2007 Co-Chair, University of California, San Francisco

Background
In the US today, there is increasing concern about the potential impacts of environmental contaminants on the reproductive health and fertility of women, men and families. In particular, there are worrisome health trends amongst the US public. For example:

In women
- At least 12% of the reproductive age population reports difficulty in conceiving and maintaining pregnancy. This appears to be a rising trend, most markedly in women under 25 years old.
- Other fertility-related diseases, like endometriosis and polycystic ovarian syndrome (PCOS), are diagnosed more frequently now, which may result from an increase in prevalence, better detection or both.

In men
- Hypospadias (deformities of the penis in infants), cryptorchidism (undescended testicles in babies) and testicular cancer are increasing while sperm count and testosterone levels are declining in certain areas and populations.
Environmental contaminants and reproductive health

In January, over 400 scientists, researchers, clinicians, health-affected groups, and community activists were brought together to discuss the current science and how to move forward to protect the health of our families – including our future health.

The Summit on Environmental Challenges to Reproductive Health and Fertility was organised by the UCSF Department of Obstetrics, Gynecology and Reproductive Sciences and the Collaborative on Health and the Environment.

One of the goals of the Summit was to start making gains in revealing the impacts of key pollutants on reproductive health – just like the understanding of the effects of environmental exposures on human health have been recognised when it comes to air pollution on cardiovascular health, and lead and mercury on our neurological development.

The participants wanted to improve their understanding of how recent science relates to clinical care, to improve communication between clinicians, patients, and the public, and to ultimately improve the policies that can protect us from exposure to environmental contaminants.

Findings from research presented at the Summit

Exposure to chemical contaminants that occur during pregnancy or during infancy are particularly powerful and are referred to as “windows of vulnerability”.

- During this time, exposure to bisphenol A found in polycarbonate plastic and can linings can cause permanent changes and increased risks of reproductive health problems later in life (infertility, miscarriage, breast cancer, prostate cancer, etc).
- Prenatal exposure to phthalates found in personal care products and products made of vinyl has been linked to reproductive effects in males, like reduced testosterone, reduce sperm count and fertility.

Cadmium is a metal, which is found in cigarette smoke and in the air, and thus we are exposed to it often.

- It is considered an endocrine disrupting chemical that can interfere with our hormones and where and how they act in our bodies – pathways important to fertility and reproduction.
- Recent research shows that cadmium in women is related to gynaecological disorders, such as endometriosis.

PFCs (perfluorinated chemicals) are common in stain proof and stick-free products and have been found in almost everyone who has been tested for them in the US.

- Prenatal exposures to PFCs can cause irreversible damage in offspring.

Health effects are starting to show up in the children of exposed mothers, fathers and grandparents.

- Some exposures can make permanent changes that are being passed from one generation to the next.

Whereas studies in animals and humans show the impacts of many of these environmental contaminants on reproductive health we are missing data for most chemicals, which makes understanding the whole picture difficult. Studies evaluate chemicals one at a time – yet we are exposed to multiple chemicals on a daily basis.

Governmental and policy changes to protect the public

Under public pressure, some governments and manufacturers are taking action to protect people from the potential dangers lurking in household products. As an example, San Francisco has introduced a ban on the production and sale of toys containing certain levels of phthalates and any level of bisphenol A (a chemical compound found in a variety of products such as food containers and dental fillings). Moreover, the European Union recently passed landmark legislation, which will regular and restrict 30,000 chemicals – over 1,100 of these are found in personal care products. The EU has also banned phthalates from toys.

This is promising progress, but there is much more to be done. Our society is increasingly chemical-dependant and therefore exposure to some toxicants is virtually unavoidable. This makes it even more important that there is information about and options for safer alternatives. Though consumers take precautions, the onus should really be on manufacturers and governmental regulatory agencies to protect the public. Without this information consumers cannot take action or make informed decisions.

Protecting the future health of women, men and families

At the Summit in San Francisco, participants identified top priorities for protecting our reproductive health:

- Enhanced research on environmental impacts
- Better testing and information on chemicals in products
- Policies for reducing exposures to chemicals.

The Summit organisers will be using the energy and information from the discussions to create a comprehensive plan for environmental reproductive health through research, education, health care and policy.

Subsequently, as our knowledge expands, we can improve communication – and science can be used to enhance policies that protect our reproductive health now and in the future!

For more information please see

www.ucsf.edu/coe/prhesummit.html
10 programme highlights
David Healy MD, President WCE 2008

1. Invited speakers
WES and AGES are very proud that every invited speaker has accepted the invitation to contribute to the 10th World Congress on Endometriosis in March 2008. Come and hear:

Mauricio Abrao
Charles Chapron
Linda Giudice
Daniela Hornung
Alan Lam
Guiseppe Matarese
Grant Montgomery
Joseph Sanfilippo
Paolo Vercellini

David Adamson
Thomas D’Hooghe
Ruth Grummer
Stephen Kennedy
Marc Laufer
Sachiko Matsuzaki
Peter Rogers
Jim Tsaltas

Michel Canis
Asgi Fazleabas
David Healy
Philippe Koninckx
Peter Maher
Stacey Missmer
Luk Rombauts
Thierry Vancaillie

2. Design of WCE 2008
WCE 2008 will have two streams: a scientific stream and a clinical stream. Late breaking news will be accommodated as 2007 advances.

3. Streams
Over the four days of the congress, each stream will consist of 12 seminars devoted to recent advances in endometriosis.

4. Maastricht revisited
WCE2008 will build upon the successful Maastricht model and will have moderator sessions. The Moderator of each topic will start with a 30 minute review of that topic, and comment on the six best abstracts chosen to address this issue. Each abstract is then presented by the submitting author, followed by (we hope!) stimulating discussion.

5. Debates
Science, medicine and humour will be presented via debates. Two speakers will each present their differing views on a current topic followed by the two best abstracts in that category. Prizes are given for the best question, best remark, best ?

6. Posters
WCE2008 welcome posters and their authors. A daily posse of WES Board Members and AGES Council Members will visit each poster for a three minute summary, followed by three minutes of questions to the first author. Prizes will be announced at the closing ceremony or the gala dinner – but remember: if you do not attend, you forfeit your prize!

7. Robot endometriosis trainee surgical workshop on 11 March
A famous AGES trainee workshop – delegates are welcome to observe young Australians learn 21st Century surgery.

8. Friday surgical workshop – a last day highlight
Cases, at various levels, operated by the members of the WCE 2008 faculty, shall be beamed live to the congress centre. There will be expert commentary at hand and instant feedback to the operating theatres available.

9. Energy
Participation in all social events, as well as the science, surgery and medicine is an AGES requirement. Come and mingle with clinicians, scientists, nurses, trainees, patients, and meet some new friends!

10. The WCE 2008 programme is available at www.wce2008.com

My lose change in my platypus piggy bank is now at $405 for that airfare…

Don’t miss our priceless articles on:

How to get over jetlag
10 Aussie traditions
10 tips to get that air fare
10 Sex facts in Australia
RESEARCH HIGHLIGHTS

Expression of inducible microsomal prostaglandin e synthase in local lesions of endometriosis patients.
Chishima F, Hayakawa S, Yamamoto T, Sugitani M, Karasaki-Suzuki M, Sugita K, Nemoto N.

Suppression of IL-1beta-induced COX-2 expression by trichostatin A (TSA) in human endometrial stromal cells.
Wu Y, Guo SW.

Multi-disciplinary centres/networks of excellence for endometriosis management and research: a proposal.
D’Hooghe T and Hummelshoj L.

Effect of a statin on an in vitro model of endometriosis.
Esfandiari N, Khazaei M, Ai J, Bielecki R, Gotlieb L, Ryan E, Casper RF.

What’s the delay? A qualitative study of women’s experiences of reaching a diagnosis of endometriosis.
Ballard KD, Lowton K, Wright JT.

The G2964A 3′-untranslated region polymorphism of the signal transducer and activator of transcription 6 gene is associated with endometriosis in South Indian women.
Bhanooori M, Deenadayal M, Kennedy S, Shivaji S.
Hum Reprod 2007 [Epub ahead of print]

Progesterone receptor polymorphism +331G/A is associated with a decreased risk of deep infiltrating endometriosis.
van Kaam KJ, Romano A, Schouten JP, Dunselman GA, Groothuis PG.

PRESENTATIONS now available online from: The art and science of endometriosis - standardizing the measurement of pain and diagnostic criteria

See also RESEARCH in endometriosis

UPCOMING MEETINGS

IFFS 19th World Congress on Fertility and Sterility
29 April - 3 May 2007
Durban, South Africa

2nd Annual Meeting of the Asian Pacific Endometriosis Alliance (APEA)
5 - 7 July 2007
Kuala Lumpur, Malaysia

16th Annual Congress of the European Society for Gynaecological Endoscopy
5 - 8 September 2007
Portoroz, Slovenia

Endometriosis and cancer
1 July 2007
Lyon, France

7th German Endometriosis Congress
26 - 29 September 2007
Berlin, Germany

10th World Congress on Endometriosis
11 - 14 March 2008
Melbourne, Australia

FULL CONGRESS SCHEDULE