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The endometriosis-ovarian cancer connection: what do the data really show?

A/Professor Paolo Vercellini
WES President

The relationship between endometriosis and epithelial ovarian cancer (EOC) has been the matter of research and debate for many years. Based on histopathology and molecular genetic alterations, EOC, which account for over 95% of ovarian cancers in general, are categorized into five main types:

- high-grade serous, 70% of EOC
- endometrioid, 10%
- clear cell, 10%
- low-grade serous <5%, and
- mucinous, 3% (1)

According to a further classification, endometrioid, clear cell, low-grade serous, and mucinous cancers are defined as type I EOC, whereas high-grade serous cancers are defined as type II EOC. It has long been known that endometriosis-associated ovarian cancers are mainly of the endometrioid and clear cell subtype, ie. type I tumours.

Several population-based studies have been published in the past two decades with the objective of defining the overall risk of EOC in women with endometriosis. Estimates vary among studies but, overall, the relative risk is between 1.3 and 1.9 in all patients with endometriosis and about 2.5 in those with associated infertility (2). Unfortunately, most analyses did not control for several factors that have an effect on the outcome, such as parity and oral contraceptive use.

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Therefore, it is difficult to definitively clarify if the association is causal or due to sharing of some risk factors such as lower parity, earlier menarche, more regular periods, and shorter cycle length (2). Indeed, the association with endometrioid and clear cell EOC is strong, with a 3- to 4-fold increase in risk, thus suggesting a continuum between endometriosis and ovarian malignancy.

Very recently, Pearce and collaborators published in Lancet Oncology the results of a pooled analysis of 13 case-control studies (3) including 7911 women with invasive ovarian cancer and 13226 controls. Respectively, 738 and 818 subjects reported a history of endometriosis. Endometriosis was associated with an overall OR of 1.46 (95% CI, 1.31-1.63) for all invasive forms; 3.5 (95% CI, 2.43-3.84) for clear cell tumours; 2.04 (95% CI, 1.67-2.48) for endometrioid ones; and 2.11 (95% CI, 1.39-3.20) for low-grade serous cancers, whereas no statistically significant association was observed with the invasive mucinous histotype, and with serous as well mucinous borderline tumours.

Where do we go from here?
In other words, should our patients be counselled differently from what we have done until now, and should our practice change?

The authors of the article published in Lancet Oncology

define endometriosis as a precursor lesion and hypothesize screening, ovarian cancer surveillance, more definitive endometriosis treatment, and risk-reduction surgery (3). However, endometriosis is just endometrium at ectopic sites. Endometrium gives rise to cancer as all the mucosae, and probably not differently than when it is located within the uterine cavity.

- Do we consider eutopic endometrium a precursor of endometrial adenocarcinoma?
- Do we suggest prophylactic hysterectomy in order to prevent endometrial cancer?

I am convinced that most of us consider only atypical endometrial hyperplasia as a precursor lesion. Similarly, only cervical intra-epithelial neoplasia, and not cervical epithelium, is the precursor lesion of cervical carcinoma, as only serous tubal intra-epithelial carcinoma, and not the fimbrial epithelium, is the precursor lesion of high-grade ovarian serous cancers.

Therefore, only atypical endometriosis, and not endometriosis in general, should be considered a precursor lesion of endometrioid and clear cell and, possibly, low-grade serous ovarian cancers.

Atypical endometriosis is observed in 2-3% of excised endometriomas, but the prevalence in the largest histology study published so far was far lower (4).

Available data consistently indicate that women with endometriosis have a modest (~50%) increase in risk of a disease with a relatively limited incidence. The lifetime risk of developing ovarian cancer varies among countries, but it is generally deemed to be around 1%.

This means that women with endometriosis have a lifetime risk of 1.5%, ie. they have 98.5% instead of 99% probability of not developing ovarian cancer.

Moreover, having endometriosis appears substantially less risky than undergoing IVF-ET, a procedure that seems associated with a three-fold increase in risk of invasive ovarian cancer (5).

Does this justify alarming our patients, organising a strict surveillance program, and offering definitive surgery in doubtful cases? How much psychological distress, surgical morbidity, and economical investment does this mean?

Furthermore, we should take into account that the available data are indeed derived from surgical series. Turning the issue the other way round, conservative surgery, which should be radical in its complete excision of the endometriotic lesions, did not prevent the increase in ovarian cancer risk. Therefore, when considering risk-reducing surgery, we must refer to salpingo-oophorectomy +/- hysterectomy. Definitive surgery may be complex, especially in patients with invasive lesions and complications should be expected. Whereas these procedures are useful in symptomatic women not responding to medical treatment, their cost/effectiveness in long-term strategies aimed at reducing mortality from ovarian cancer has yet to be demonstrated. Meanwhile, let me recall the "chemotherapeutic" use of oral contraceptive that, when taken for some years, reduce the risk of ovarian cancer by even 80% specifically in women with endometriosis (6).

In conclusion, our goal for the future should be identification of high-risk women based on previous demonstration of atypical endometriosis or, possibly, genotypic characteristics still to be determined. Based on the available data, risk-reducing surgery, when conception is no more an issue, should be an option for them, but not for all women with endometriosis. Future studies are eagerly needed to identify characteristics that could further define the population at increased risk, including the role of endometriotic lesion type.

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The threat of cancer raises its ugly head ... again!

It was all over the newspapers: the link between endometriosis and ovarian cancer. Headlines went from "Endometriosis increases the risk of cancer" to "Endometriosis causes cancer". The cause of the media interest this time was the recent publication of a study in the Lancet Oncology by Pearce and coworkers (1). They presented their findings of a pooled analysis of 13 case-control studies and make and made recommendations that raised an eyebrow here and there.

Our current president, Paolo Vercellini, has previously written in this journal on the topic of endometriosis and cancer (2). In this issue he comments again on the sense and non-sense of this current debate. His thoughtful analysis of our current understanding of the link between the two is very helpful for anyone who deals with patients who may have become anxious because of the news reports. Another critical view of the conclusions of the new report can be found on the blog of Marya Zilberberg. Her calculations on how the new estimates of cancer risk affect the risk of a false positive in a ovarian cancer screening program are worth a read.

At times like these, as a clinician, I think it is important to emphasize once more how important it is to be part of a learned society like the WES. Whatever happens in your practice, you can always rely on the fact that you are up to date with the current thinking in the diagnosis and management of endometriosis in all its presentations. Consider talking to your colleagues and ask them to become a member so we can grow the World Endometriosis Society for everyone' sake.

In this issue of the eJournal we also welcome the first contribution of one of our newly elected Board Members: Professor Kathy Sharpe-Timms from the The University of Missouri. For most of you Kathy does not need introducing. Her work on matrix metalloproteinase enzymes and their inhibitors is well-known. We are grateful for her summary of this field in the context of Sampson's theory of retrograde menstruation (page 4).

We further celebrate Professor Linda Giudice's elevation to Fellow of the American Association for the Advancement of Science (AAAS). Linda will join 40 other highly distinguished leaders in the field of medical science who accepted their new fellowship at the AAAS Annual Meeting, on 18 February 18 2012 in Vancouver, Canada. Read more on page 10.

A/Professor Luk Rombauts
WES eJournal Editor

We also highlight the fact that endometriosis has been addressed at a legislative level in the United States for the first time. The World Endometriosis Research Foundation's chief executive, Lone Hummelshoj, was invited as a keynote speaker, where she addressed the Women in Government's 2nd Annual Healthcare Summit in November 2011 (report available online).

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Minutes from the World Endometriosis Society's 2011 General Assembly are **available on our website**

Endometriosis: Sampson's Theory, the rest of the story

by Professor Kathy L Sharpe-Timms, PhD
Department of Obstetrics, Gynaecology and Women's Health,
Division of Reproductive and Perinatal Research
The University of Missouri, Columbia, USA
timmsk@health.missouri.edu

Professor Kathy L Sharpe-Timms

Introduction

Endometriosis, the presence of tissue containing endometrial glandular epithelial and stromal cells outside the uterine cavity, plagues women of reproductive age with debilitating pain and subfertility. Despite the physical, psychological, social and economic costs of endometriosis, medical and surgical therapeutic approaches remain suboptimal and are often accompanied by rapid, spontaneous recurrence. A logical approach to overcoming these deficiencies would include a definitive understanding of the mechanistic origins of endometriosis, such that novel, curative and preventative interventions may be developed. For more than a century pioneers in the field of endometriosis have proposed numerous, often controversial theories for the origins of endometriosis (reviews: Vinatier D et al, 2001; Giudice L and Kao LC, 2004; Robboy and Bean, 2010; Jiang and Wu, 2012). The focus here will be on Sampson's Theory of Retrograde Menstruation and Implantation and the studies supporting etiopathogenic mechanisms necessary to validate this theory.

Sampson's Theory

Sampson's Theory of Retrograde Menstruation and Implantation postulates endometrial cells from menstrual effluent are refluxed through the Fallopian tubes into the abdominal cavity with subsequent implantation in the peritoneum (Sampson, 1927a, b). Evidence supporting Sampson's Theory implicates attachment of retrogradely shed menstrual tissue to a peritoneal surface, invasion into extracellular matrices, escaping immune surveillance and establishment of a vascular network to persist in endometriotic lesions in ectopic sites (reviews: Vinatier et al, 2001; Jiang et al, 2012).

Attaching shed endometrial tissues to the peritoneum

There is evidence that shed endometrial tissues may attach to the peritoneal surface via cell adhesion molecules such as integrins or via CD44 / hyaluron interactions (Figure 1A). Eutopic stromal cells from women with endometriosis exhibit an aberrant integrin profile in vitro compared with stromal cells derived from healthy controls (Klemmt et al, 2007). The former display increased adhesion and proliferative capacity in response to specific ECM components and may contribute to the predisposition of some women to the disease. Shed endometrial tissues express CD44, a cell-surface glycoprotein involved in a wide variety of cellular functions such as cell-cell interactions, cell adhesion and migration. CD44 serves as the primary receptor for hyaluron (HA). Peritoneal cells secrete HA, a glycosaminoglycan. There is growing evidence that the interaction between CD44 and HA is involved in the attachment of endometrial cells to peritoneal mesothelial cells (Figure 1A; Dechaud et al, 2001; Griffith et al, 2010). Deglycosylation of N- and O-linked sites decreases attachment of endometrial cells to peritoneal cells suggesting a role for CD44 N- and O-linked glycosylation in the development of early endometriotic lesions (Rodgers et al, 2011). Blocking integrins or altering post-translational modifications of CD 44 may serve as a way to inhibit adherence of shed menstruum to the peritoneum.

Invading the extracellular matrix (and altering fecundity)

After attachment, shed endometrial cells must invade into the extracellular matrix (ECM) of the peritoneum. Matrix metalloproteinase enzymes (MMPs) are a

multifamily group with members each having great variability, which provides ECM degradation in both normal and pathophysiological conditions, including endometriosis (review: Amălinei et al, 2010). The functions of MMPs and their inhibitors (tissue inhibitors of metalloproteinases, TIMPs) in endometriosis as well as mechanisms controlling their regulation in the pathogenesis of endometriosis have been reviewed numerous times (reviews: Osteen et al, 1996, 2003; Sharpe-Timms and Cox, 2002; Zhou and Nothnick, 2005; Bondza et al, 2009; Amălinei et al, 2010). Precise choreography of expression and action of MMPs and TIMPs is required for controlled tissue remodelling; where misexpression of several MMPs and TIMPs provide insight into the invasion of shed endometrial tissues in ectopic locations. The principle would be that excess MMPs may cause or facilitate tissue remodelling necessary for the establishment of endometriotic lesions (Figure 1B).

Endometriotic lesions synthesize and secrete TIMP1 into the peritoneal cavity in women and in an animal model for endometriosis (Sharpe et al, 1995), which we proposed reduced fecundity (Stilley et al, 2009). Using an in vivo endometriosis model in rats, we found fewer follicles and corpora lutea plus the presence of luteinized unruptured follicles (LUFs). TIMP1 of endometriotic origin binds to the theca layer of ovarian follicles and impedes follicular development and ovulation and binds to the perinuclear region of preimplantation embryos and reduces development (Stilley et al, 2009, review: 2012). Foretelling of a possible treatment to restore fertility in women with endometriosis, a function blocking TIMP1 antibody restored ovarian dynamics and embryo quality in this endometriosis model, whereas TIMP1 treatment bestowed a subfertile endometriotic phenotype in controls (Stilley et al, 2010; Stilley and Sharpe-Timms, 2011). Most interestingly, daughters of these endometriosis rats that had no experimental interventions also exhibited similar reproductive abnormalities (Stilley et al, 2009, Birt et al, 2011).

And while TIMP1 may block the MMPs as a counteractive mechanism for invasion, TIMPs have other non-MMP dependent functions which may play a role in the pathogenesis and pathophysiologies of endometriosis. The N-terminal domain of TIMP1 and TIMP2 is sufficient for inhibition of MMPs in tissue remodelling (Figure 1C). However, unique MMP-independent features of TIMPs in regulation of apoptosis, cell growth, immunomodulation and angiogenesis are facilitated in part by specific protein-protein interactions mediated by the TIMP1 C-terminal domain (Figure 1C; Lambert et al, 2004; Chirco et al, 2006; Stilley and Sharpe-Timms, 2011; reviews: Stetler-Stevenson, 2008; Stilley et al, 2012). MMP-independent functions of TIMPs C-terminal may also be a part of a mechanism by which excessive TIMP1 from endometriotic lesions affects fecundity in women.

Hence, MMPs and TIMPs play a role in tissue remodelling in the establishment and pathophysiologies of endometriosis-related subfertility by classical and non-classical mechanisms. Research into these mechanisms should provide a myriad of diagnostic and therapeutic approaches to eliminate existing disease and its symptoms and possibly prevent shed endometrial tissues from establishing new endometriotic lesions.

Avoiding immune surveillance

Shed endometrial tissues in the peritoneal fluid of women must also avoid immune surveillance and destruction. Macrophages, T and B lymphocytes and natural killer cells seem to play essential roles in determining either accept or reject survival, implantation, and proliferation of endometrial and endometriotic cells (Sharpe-Timms et al, 2005, 2010; Osuga et al, 2011; Berbic et al, 2011). Adherence of macrophages, the first step in phagocytosis, is significantly diminished through binding of a uniquely glycosylated form of haptoglobin produced by endometriotic lesions, shed menstruum and eutopic endometrium from women with endometriosis but not those without endometriosis (Sharpe-Timms et al, 2002, 2005, 2010). Others have shown a reduced activity of cytotoxic T cells and NK cells, cytokine secretion by helper T cells, and autoantibody production by B lymphocytes in women with endometriosis (Osuga et al, 2011; Berbic et al, 2011; Sikora, 2011; review: Olovsson, 2011) Also, NF-kB transcriptional activity modulates inflammatory cell function contributing to the initiation and progression of endometriosis (González-Ramos et al, 2011).

Establishing a vascular network

Long-term survival and proliferation of endometriotic lesions is notably dependent on angiogenesis, the ingrowth of new blood vessels from the surrounding host tissue, which guarantee oxygen and essential

nutrient supply (Groothuis et al, 2005; Laschke and Menger, 2007; May and Becker, 2008; review: Taylor et al, 2009). The proposed mechanisms of angiogenesis are diverse and require further characterisation for development of anti-angiogenic treatments. In addition to angiogenesis, new blood vessels may also develop from circulating endothelial progenitor cells (EPCs), which are recruited and incorporated into the sites of neovascularization (Asahara et al, 1997; review: Laschke et al, 2011). A current review of the current literature by Laschke and colleagues (2011) highlights this process, called post-natal vasculogenesis, as an integral part of the pathogenesis of endometriosis. It has been proposed that TIMP1 also stimulates growth of new vasculature (Stilley and Sharpe Timms, 2011).

Eutopic endometrium: the missing link?

It has long been known that most women have some degree of retrograde menstruation, yet only a portion of women develop endometriosis (Halme et al, 1984; Kruitwagen et al, 1991; Sharpe-Timms et al, 2005). So what mitigating factors cause or allow interaction between shed endometrium and the peritoneum to form endometriotic lesions in some women and not others? Might this be related to the quantity, quality or characteristics of the shed menstrum?

A long list of endometrial anomalies has emerged which support fundamental differences in the eutopic endometrium of women with endometriosis compared to that of women without endometriosis, which may contribute to the pathogenesis of this condition and support Sampson's Theory (Hill LL Jr, 1932; Klemmt et al, 2007; Aghajanova and Giudice, 2011; Rodgers et al, 2011; reviews: Sharpe-Timms, 2001, Vinatier et al, 2001; Ulukus et al, 2006; Bondza et al, 2009; Carvalho et al, 2011). Intrinsic endometrial abnormalities thought to be associated with endometriosis include genetic predisposition, modification of endometrial response to hormones such as progesterone; increased nerve density, and oxidative stress (review: Carvalho et al, 2011). A host of other aberrantly expressed genes and their protein products from endometriotic lesions, such as MMPs and TIMPS, Hox genes, integrins, anti-apoptotic genes Bcl-2, steroid hormones, immuno-inflammatory factors and angiogenic factors, have been identified (review: Bondza et al, 2009). Inflammatory pathways have also been found to cause endometrial disorders and lead to endometriosis (review: Maybin et al, 2010).

Others have hypothesised that an increase in telomerase production in sloughed endometrium has enhanced replicative capacity, which aids in the establishment of ectopic lesions (Hapangama et al, 2008). And many of these anomalies, which are supported by data from animal models and in vitro cell culture or from women with and without endometriosis, have clinical correlations with the objective of understanding the role of eutopic endometrium in endometriosis (review: Carvalho L et al, 2011).

What causes normal endometrium, endometrial stem cells and embryonic origins of endometriosis to possibly go awry?

As noted, endometriosis does not occur in all women. For those women afflicted, endometriotic lesions appear in variable numbers and phenotypes and cause unpredictable levels of pain and/or subfertility. What might happen to a woman or group of women, which predisposes their endometrium toward of development of endometriotic lesions? Table 1 provides a summary of possible etiopathogenic mechanisms causing endometrial (and other) anomalies and the evolution of endometriotic lesions assembled from recently published reviews, years 2009 to 2012. Any of these anomalies may work alone or in consort to lead to the development of endometriosis.

Summary

Credence in each theory explaining the origin of endometriosis has cyclically waxed and waned over the years. New insights from innovators in modern science, with novel medical and technological developments, help unravel cellular and molecular mechanisms and pathways involved in the pathogenesis and pathophysiologies of endometriotic lesions. From this and other evidence, it would seem plausible that novel therapeutic paradigms and possibly curative methods may be developed as alternatives to the current, temporary and sometimes counterproductive medical or surgical approaches for treatment of endometriosis.

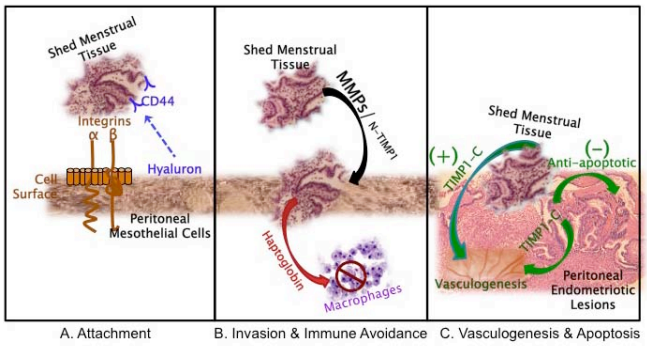

Figure 1. Evidence Supporting Sampson's Theory

A. Attachment: Shed endometrial tissues attach to surface peritoneal mesothelial cells via integrins (brown) and/or interaction between peritoneal cell hyaluron and shed tissue CD44 expression (blue).
B. Invasion & Immune Avoidance: Shed endometrial tissues invade into the peritoneal cell layers via an imbalance of MMPs and N-terminal TIMP action (black), favouring the enzymatic activity of the MMPs. New and established endometriotic lesions express haptoglobin (red) which interferes with macrophage phagocytosis of ectopic endometrium (red).
C. Vasculogenesis and apoptosis: TIMP1 from eutopic endometrium and endometriotic lesions, stimulates vasculogenesis (green), blocks apoptosis (Green), and has other C-terminal, MMP-independent functions favouring establishment of endometriosis (not shown).

Table 1: Etiopathogenic mechanisms leading to endometriosis

Mechanisms	References
Endometrial Stem Cells	Garry et al, 2009; Maruyama et al, 2010, Figueira et al, 2011; Oliveira et al, 2012
Embryonic origins of endometriosis	Signorile et al, 2010a, 2010b, 2011; Matsuzake and Darcha, 2012
Genetic and genomic inheritance	Guo, 2009; Hansen and Eyster, 2010; Abu-Asab et al, 2011
Epigenetic modifications	Guo, 2009; Borghese et al, 2010; Ruma, 2010; Kawano, 2011; Peltomäki and Butzow, 2011; Nasu et al, 2011
Endocrine disorders	Bulun, 2009
Altered immunity and inflammation	Cakmak et al, 2009; Lousse et al, 2012
Dietary and environmental influences and endocrine disruptors	Bellelis et al, 2011

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Upcoming meetings

22nd European Congress of Obstetrics and Gynaecology	**9 – 12 May 2012 Tallinn, Estonia**
10th International Scientific Congress (RCOG 2012)	**6 – 8 June 2012 Kuching, Malaysia**
3rd International Congress by the International Society of the Fallopian Tube and Reproductive Surgery (ISFT-RS)	**8 – 9 June 2012 Leuven, Belgium**
Joint ASRM/ESHRE pre-congress course on "Endometriosis and pain"	**1 July 2012 Istanbul, Turkey**
28th Annual Meeting of ESHRE	**1 – 4 July 2012 Istanbul, Turkey**
4th Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2012)	**30 August – 2 September 2012 Osaka, Japan**

Contributions to the next issue of the eJournal should be with us by **2 May 2012**
ejournal-editor@endometriosis.org

WES President Elect Linda Giudice honoured by the AAAS

WES President Elect, Professor Linda Giudice, has been awarded the distinction of fellows by the American Association for the Advancement of Science (AAAS) for her scientific research in reproductive medicine, statistics, and stem cells.

Professor Giudice is a biochemist, gynaecologist, and reproductive endocrinologist who specialises in endometriosis, implantation and ovulatory disorders, infertility, and assisted reproduction.

She is President Elect of the ASRM; Vice President of the World Endometriosis Research Foundation; a leader in research on the environmental impacts on reproductive health and founder of the UCSF Program on Reproductive Health and the Environment (PRHE); and a former president of the Society for Gynaecologic Investigation (SGI).

Professor Giudice has served on numerous NIH study sections, is the former Chair of the Reproductive Health Drugs Advisory Committee to the FDA, and chaired the NIH Reproductive Medicine Network and Specialised Cooperative Centers Programme in Reproduction and Infertility Research Steering Committees. She was elected to the Institute of Medicine of the National Academies in 2002 and is currently a member of the IOM Health Sciences Policy Board. In 2011, Professor Giudice was elected Co-Chair of the NICHD Director's Reproduction Vision Workshop.

Giudice's contribution to reproductive science

In her research, Professor Giudice focuses on endometrial biology and placental-uterine interactions relevant to implantation and pregnancy disorders, environmental impacts on reproductive health (including endometriosis), and human embryonic and endometrial stem/progenitor cells.

Professor Giudice is the recipient of numerous awards for her work including the 2008 SGI President's Distinguished Scientist Award, the 2008 Women in Science Award from the American Medical Women's Association, and the ASRM 2008 Distinguished Researcher Award.

Professor Linda Giudice
WES President Elect

She was honoured as one of the NIH Great Teachers and the NIH Perinatology Branch Wall of Honour. She is also the recipient of the American Infertility Association "Illumination Award" for her work on the environment and reproductive health.

The AAAS fellowship recognises Professor Giudice's distinguished contributions to the field of reproductive medicine and reproductive science, including endometrial biology, environmental impacts on reproductive health (including endometriosis), infertility, and human embryonic and endometrial biology.

Mark your diaries now: don't miss the 12th World Congress on Endometriosis

We are proud to host and welcome you to the **XII World Congress on Endometriosis**: Adding pieces to the puzzle of endometriosis, 30 April - 3 May 2014 in São Paulo, Brazil.

Brazilians have been contributing significantly to research in endometriosis. In more recent WCE meetings, submitting the largest number of abstracts in Maastricht in 2005, and again in Montpellier with 16% of the total number of abstracts received. Brazilians were also the most numerous in Melbourne in 2008, where we carried off the Rodolphe Maheux Award. In short: we are serious about endometriosis in Brazil!

Professor Maurício Simões Abrão
WCE2014 President

As the largest, most cosmopolitan and wealthiest city in Latin America, São Paulo and its multicultural background can offer a unique experience for the WCE participants. In June 2014 São Paulo will host some of the FIFA Soccer World Cup as well. The city should then have substantially improved its overall infrastructure and services to facilitate access to its internationally acclaimed restaurants and hotels, and to the nearby beaches and mountains.

You can keep with all news of the 12th World Congress on Endometriosis on our website: www.endometriosis.ca/wce2014 or follow us on Twitter: www.twitter.com/WorldEndoSoc.

We look forward to welcoming you to a memorable experience!

Maurício Simões Abrão

President
12th World Congress on Endometriosis

12TH WORLD CONGRESS ON ENDOMETRIOSIS

30 April to 3 May 2014 - Sao Paulo, Brazil
www.endometriosis.ca/wce2014

World Endometriosis Society • Central Business Office • 89 Southgate Road
London • N1 3JS • England • t +44 (0)77 1006 5164
www.endometriosis.ca • wes@endometriosis.ca
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