Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France

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Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France

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Abstract

Endometriosis, defined as estrogen-dependent lesions containing endometrial glands and stroma outside the uterus, is a chronic and often painful gynecological condition that affects 6% to 10% of reproductive age women. Endometriosis has estimated annual costs of US $12 419 per woman (approximately €9579), comprising one-third of the direct health care costs with two-thirds attributed to loss of productivity. Decreased quality of life is the most important predictor of direct health care and total costs. It has been estimated that there is a mean delay of 6.7 years between onset of symptoms and a surgical diagnosis of endometriosis, and each affected woman loses on average 10.8 hours of work weekly, mainly owing to reduced effectiveness while working. To encourage and facilitate research into this debilitating disease, a consensus workshop to define future directions for endometriosis research was held as part of the 11th World Congress on Endometriosis in September 2011 in Montpellier, France. The objective of this workshop was to review and update the endometriosis research priorities consensus statement developed following the 10th World Congress on Endometriosis in 2008.[1] A total of 56 recommendations for research have been developed, grouped under 6 subheadings: (1) diagnosis, (2) classification and prognosis, (3) clinical trials, treatment, and outcomes, (4) epidemiology, (5) pathophysiology, and (6) research policy. By producing this consensus international research priorities statement, it is the hope of the workshop participants that researchers will be encouraged to develop new interdisciplinary research proposals that will attract increased funding support for work on endometriosis.

Keywords

endometriosis, research directions, international workshop, consensus report

Introduction

As part of the 11th World Congress on Endometriosis (WCE) held in Montpellier, France, in September 2011, a World Endometriosis Society (WES) and World Endometriosis Research Foundation (WERF) workshop of interested persons was convened to review and update the consensus statement produced at the 10th World Congress of Endometriosis in 2008.[1] Its objective was to derive a global consensus statement defining future directions for endometriosis research. The format for the meeting was 6 sessions covering different endometriosis-related topics with expert moderators responsible for each session. Each moderator was asked to briefly review what progress has been made for their topics in the last 3.5 years, discuss whether the 2008 recommendations needed updating, and make suggestions for and lead the discussion on new/revised recommendations. Each moderator was responsible for producing a written summary listing and justifying research recommendations for their session which was then incorporated into this final

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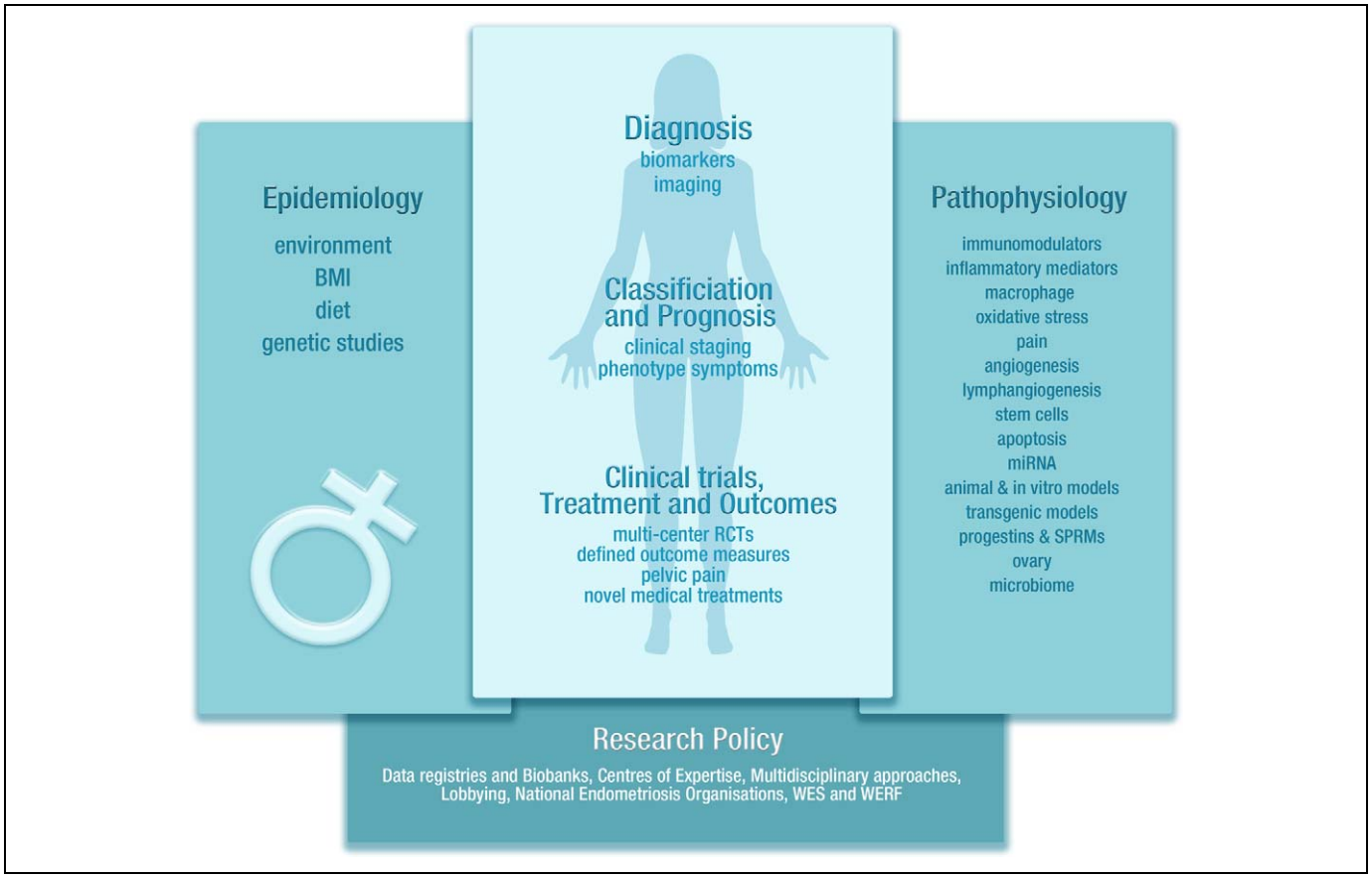

Figure 1. Summary of the key areas addressed in Endometriosis Research Directions international consensus workshop.

report. The workshop was attended by 58 participants from 19 different countries representing a wide spectrum of interests and expertise from clinical through fundamental research to patient advocates and women with endometriosis.

Given the complex and multidisciplinary nature of endometriosis, the philosophy of the workshop was to be as inclusive as possible in adopting recommendations for research. Although by no means proscriptive, it is hoped that these recommendations will act as both a guide and a stimulus to the international research community as well as the many funding agencies that may provide support for endometriosis research. A total of 56 recommendations for research have been developed, grouped under 6 subheadings: (1) diagnosis, (2) classification and prognosis, (3) clinical trials, treatment and outcomes, (4) epidemiology, (5) pathophysiology, and (6) research policy (Figure 1).

Background

Endometriosis is a chronic gynecological disorder that is defined as estrogen-dependent lesions containing endometrial glands and stroma outside the uterus. It occurs on the peritoneum and ovaries, in the rectovaginal septum, and in other sites within and outside the pelvis. It may be asymptomatic or associated with symptoms of pain and/or infertility.[2] Endometriosis affects an estimated 6% to 10% of women in the reproductive age group.[3] This prevalence increases up to 30% in women with infertility[4] and to 50% in infertile women with a normal cycle whose partner has normal sperm.[5]

Recently, through the WERF, the first ever prospective study investigating the direct and indirect costs of endometriosis in 10 countries estimated annual costs of US $12 419 per woman (approximately €9579), comprising one-third of the direct health care costs with two-thirds attributed to loss of productivity.[6] Decreased quality of life (QoL) was the most important predictor of direct health care and total costs. This study confirmed that the economic burden associated with endometriosis treated in referral centers is high and is similar to other chronic diseases (diabetes, Crohn disease, rheumatoid arthritis). These results are in agreement with an earlier prospective study of 1418 women with and without endometriosis.[7] This work showed that there was a delay of mean of 6.7 years, principally in the primary care, between onset of symptoms and a surgical diagnosis of endometriosis, and that endometriosis caused a significant impact on health-related QoL (HRQoL). Each affected woman lost on average 10.8 hours of work weekly, mainly owing to reduced effectiveness while working. Loss of work productivity translated into significant costs, ranging from US $208 in Nigeria to US $23 712 in Italy per woman per year.

Between the 2008 and 2011 WCE meetings, a total of 3176 new scientific publications on endometriosis were recorded on

PubMed. This represents a 21.5% increase in the total number of scientific papers published prior to 2008 in the field, an indication that significant research effort exists around this problem. The vast majority of the publications were in established areas of endometriosis research, including etiology, surgery, histology, pathology, pain, cancer, and fertility, although a number of emerging endometriosis research fields had significantly increased publication rates including stem cells, proteomics, genomics, angiogenesis, vasculogenesis, genetics, and inflammation.

Although it can sometimes be difficult to predict the future impact of scientific publications at the time they first appear, there were some publications over the past 3 years that could readily be identified as major contributions. These include the first 2 genome-wide association (GWA) studies for endometriosis[8,9] and ongoing work in the area of nerve fibers and endometriosis.[10] Undoubtedly there are others.

Diagnosis

In patients with clinical suspicion of endometriosis, diagnostic laparoscopy has been shown by subsequent histopathological testing to confirm the diagnosis in 78% to 84% of the patients,[11,12] although significantly lower rates than this have also been reported.[13-15] Diagnostic laparoscopy is an excellent tool for direct visualization of the pelvis and may help identify the etiology of the patients' pain,[16] and surgical ablation of disease can occur in the same procedure. However, the quality of the available literature on the efficacy of diagnostic laparoscopy as it relates to patient outcome is limited, as almost all of the available studies are retrospective studies from single institutions. Furthermore, there is a paucity of data on long-term outcomes and little data on cost-effectiveness and QoL.[16] Procedure-related complications from laparoscopy include bowel injuries, bleeding, urological injuries, vaginal cuff wounds, peritonitis, and pelvic pain. The risk of complications is related to the complexity of surgery and the experience of the laparoscopist. In a large multicenter French study (n = 29 966), diagnostic and therapeutic laparoscopy were found to be associated with a 3.3 per 100 000 mortality and a 4.6 per 1000 morbidity risk.[17]

A noninvasive test for the reliable diagnosis of endometriosis, and in particular early endometriosis, remains a priority. Specificity and sensitivity of any diagnostic test are key issues, with many patients having comorbidities, such as adenomyosis, irritable bowel syndrome, and interstitial cystitis, which can all contribute to the symptomatology. Because of the likely variable etiology of endometriosis, different subsets of biomarkers may be required for different stages and/or clinical classifications of endometriosis. A recent systematic review of 182 relevant articles that assessed over 200 potential biomarkers identified several reports of endometrial differences which have the potential to be biomarkers for endometriosis. However, the authors concluded that larger studies in well-defined populations are required to determine their true usefulness.[18] More recently it was reported that in plasma samples obtained during menstruation, multivariate analysis of 4 biomarkers (annexin V, VEGF, CA-125, and sICAM-1/or glycodelin) enabled the diagnosis of endometriosis undetectable by ultrasound with a sensitivity of 81% to 90% and a specificity of 63% to 81% in independent training and test data sets.[19] Peptide fingerprinting using proteomic analysis of plasma may also have utility as a noninvasive or semi-invasive diagnostic for endometriosis.[20] Taken together, these data suggest that endometriosis biomarkers can be developed using a panel of "known" biomarkers or by the discovery of new biomarkers based on proteomic, microarray, metabolomic analysis, or other systems biology approaches.

Recommendation

Discovery and identification of new and validation of existing endometriosis-associated biomarkers is required to develop an accurate, noninvasive method to diagnose endometriosis.

The different clinical classifications of endometriosis need to be taken into consideration as part of the evaluation of predictive and diagnostic biomarkers.

Different techniques for diagnostic and preoperative imaging of endometriosis are being explored, including ultrasound, computed tomography, and magnetic resonance imaging.[21] From a clinical point of view, the ideal is a test with high sensitivity that does not miss any individuals with endometriosis or other pelvic conditions that might benefit from diagnostic or operative laparoscopy.[22] Although the resolution of imaging techniques continues to improve, their current diagnostic accuracy remains significantly inferior to direct laparoscopic visualization. Other issues associated with imaging of endometriosis are the training required to achieve acceptable sensitivity and specificity rates, and the cost of these procedures if used as a screening tool.

Recommendation

Advances in imaging techniques should be monitored for application to diagnosis of endometriosis.

Classification and Prognosis

In the broadest sense, classification may be related to the risk of endometriosis, the etiology of the disorder (including genetic and environmental factors), disorders associated with endometriosis, targeting therapies, and designing inclusion/exclusion criteria for clinical trials to evaluate diagnostics and therapeutics. The revised American Fertility Society (rAFS) classification of endometriosis [23] and the revised American Society for Reproductive Medicine classification of endometriosis, 1996 [24] have been the most widely used classification criteria for endometriosis. However, these classifications are restricted to a limited number of criteria and are not particularly valuable for predicting many of the parameters needed for clinical management, including pain or fertility outcomes. A refinement of the rAFS/rASRM criteria is the ENZIAN classification system,

developed to describe more severe disease.[25] However, this classification system does not appear to be widely used. Currently, The American Association of Gynecologic Laparoscopists is developing a categorization system that will be more focused on pain.[26]

There has been recent progress in the development of a prognostic algorithm for fertility following surgery for endometriosis. The endometriosis fertility index (EFI) is a clinical tool that predicts pregnancy rates in patients with surgically documented endometriosis who attempt non–in vitro fertilization conception.[27] The EFI is a simple, robust, and validated clinical tool that provides reassurance to those patients with good prognoses and avoids wasting time and treatment for those with poor prognoses.

One difficulty recognized by workshop participants in developing classification and prognostic tools for endometriosis was the need to broaden the criteria to include more than just surgical findings and to attempt to better define some of the more variable disease attributes.

Recommendation

To collect data and evaluate across populations the phenotypic appearance of disease, the symptomatology of disease, and attempt to more finely characterize, beyond our current staging system, differences between women.

Recommendation

The WES and the WERF investigators should establish a task force to consider clinical staging based on combinatorial algorithms incorporating historical findings (including prior therapies), presenting symptoms (pain and infertility), and intraoperative and biochemical findings.

Clinical Trials, Treatment, and Outcomes

Current treatment options for women with endometriosis-associated pain and/or infertility include surgery, medical treatment, alternative therapies, and assisted reproduction. Professional guidelines for the clinical management of endometriosis have been developed,[28-32] and it is important to ensure that these guidelines are continually reviewed and updated to reflect the latest clinical and scientific findings, and that they are adopted by health care professionals worldwide.

Surgery is often considered the best treatment option for women with symptomatic endometriosis. However, the extent and duration of the therapeutic benefit are still poorly defined.[33] Methodological drawbacks limit considerably the validity of observational, noncomparative studies on the effect of laparoscopy, identifying the need for prospective, multicenter randomized controlled trials. Based on a review of best available evidence, pain recurrence and reoperation rates after conservative surgery for symptomatic endometriosis are high and probably underestimated. Clinicians and patients should be aware that the expected benefit is also operator dependent.[33]

A number of research questions developed at the WCE research directions workshop in 2008 remain valid today, including (1) whether effective medical adjuvant therapies exist to prevent or limit the recurrence of lesions and symptoms following surgery, (2) whether laparoscopic ablation or excision of endometriosis is more effective in women with pain, (3) whether the introduction of advanced operative laparoscopy techniques have resulted in an increase in adverse outcomes relating to long-term bladder, bowel, or ovarian dysfunction, and (4) whether such techniques are superior to more conservative surgery in preventing long-term recurrence of endometriosis.

It was also noted that surgical and clinical trials offer an excellent opportunity to obtain well-characterized tissue samples for collaborative studies on the pathophysiology of endometriosis.

Recommendation

There is a need for more well-designed, adequately powered, multicenter randomized controlled trials and long-term follow-up studies comparing different endometriosis treatment options against defined outcome measures.

Recommendation

Clinical trials in endometriosis should focus on outcomes of high relevance to women, that is, quality of life and key fertility outcomes including live births.

Recommendation

We need to transform our clinical study design to integrate treatment failure for the first agent, with subsequent rescue agents in a phased, organized, and stratified manner.

Major advances in improving understanding and alleviating pain in endometriosis will likely occur if the focus changes from lesions to pain. In turn, how endometriosis affects the central nervous system (CNS) would be best examined in the context of mechanisms underlying other chronic pain conditions.[34]

Recommendation

Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including inflammatory nociceptic, neuropathic, and central pain.

There is only limited evidence to support the use of progestagens and antiprogestagens for pain associated with endometriosis.[35] New hormonal and nonhormonal therapies are continually being developed for the treatment of endometriosis-related pain. The state of advancement and the results of novel treatments studied in registered trials (www.ClinicalTrials.gov) have recently been reviewed.[36] Cellular signaling pathways activated in endometriotic cells, which constitute potential targets for future treatments, are also described. Therapeutic research efforts should focus on

identifying and testing substances capable of acting locally on the lesions themselves, without interfering with ovulation, in order to be efficacious on both pain symptoms and infertility.

In China, treatment of endometriosis using Chinese herbal medicine (CHM) is routine, and considerable research into the role of CHM in alleviating pain, promoting fertility, and preventing relapse has taken place. There has been a recent Cochrane Systematic Review of the effectiveness and safety of CHM in alleviating endometriosis-related pain and infertility.[37] The authors concluded that post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol; it may be more effective in relieving dysmenorrhea and shrinking adnexal masses when used in conjunction with a CHM enema. However, more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.

Recommendation

Novel medical treatments for endometriosis should be investigated.

Endometriosis occurs in adolescents, and presenting symptoms may vary from those seen in adult women with the disease.[38] Laparoscopic surgery and long-term medical therapy are current options to decrease pain and the progression of the disease, thus decreasing the risk of advanced-stage disease and infertility.

Recommendation

Investigate the link between dysmenorrhea and endometriosis and early intervention strategies in younger women.

A recent retrospective study of pregnancy outcome in women with peritoneal, ovarian, and rectovaginal endometriosis found elevated levels of miscarriage, ectopic pregnancy, gestational hypertension/preeclampsia, preterm delivery, placental abruption, and placenta praevia.[39,40]

Recommendation

Studies on pregnancy and pregnancy outcomes in women with endometriosis need to be undertaken.

Epidemiology

Genetic and environmental factors contribute to endometriosis risk and the disease is inherited as a complex trait.[41-45] Candidate gene studies have reported association between endometriosis and markers in many genes. Results have generally not been replicated in subsequent studies,[41,46-48] and variability between studies led to concerns about the estimates of genetic contribution to disease risk. However, studies in Australian twins,[45] in the Icelandic population,[43] and in rhesus macaques [49] provide strong evidence for a genetic contribution to the disease with the heritability of endometriosis estimated to be around 50%.[45] Lack of replication for many candidate gene studies is likely due to issues with study design including the lack of power in small-scale studies that detect only variants with large effect and are prone to detection of false positive results, differences in disease definitions, and case–control population sampling issues.[50]

Large GWA studies have been a powerful approach to discover genes influencing the risk of many common diseases. Generally, DNA samples are genotyped with representative single-nucleotide polymorphisms from across the genome and allele frequencies compared between cases and controls. A study in samples from Japanese women (1423 cases and 1318 controls) from the BioBank Japan[9] reported GWA in the noncoding RNA *CDKN2BAS* on chromosome 9p21.3. The International ENDOGENE study in a European Caucasian sample from Australia (2270 cases and 1870 controls) and the Unites Kingdom (924 cases and 5190 controls)[8] identified significant association in an intergenic region on 7p15.2. The ENDOGENE study also replicated evidence for association near the *WNT4* gene on 1p36.12 previously reported in the Japanese study.[8,9]

Association results must pass stringent thresholds for significance and be replicated in independent studies before evidence for association with disease risk is accepted. Only a few of the top signals in GWA studies meet these criteria. Many other variants with signals just below the significance threshold will be "truly" associated with disease, although these cannot be distinguished from the false positive signals. Methods can be applied to data from genome scans to use predictive information from markers representing "true" signals to evaluate the genetic contribution to disease subtypes and genetic comorbidity with other diseases. Analysis of the International ENDOGENE data provided independent evidence for a genetic contribution to disease risk supporting results from earlier family-based studies.[8,43-45] The results also demonstrated stronger genetic loading of moderate to severe (stage B) endometriosis (rAFS stage III or IV disease) compared to minimal (stage A) endometriosis (rAFS stage I or II disease)[8]. These results represent the first convincing evidence for gene regions associated with endometriosis risk, strongly support evidence from family-based analysis for genetic contributions to endometriosis, and demonstrate how GWA marker data can be used to evaluate genetic contributions to disease subgroups.

Evidence from many complex traits show that the number of variants discovered is strongly correlated with experimental sample size.[51] Above a given threshold for each disease, doubling study size doubles the number of genes or regions identified. The GWA studies have been successful in endometriosis despite modest sample sizes when compared to many other disease studies. Increasing the sample size for genetic studies in endometriosis will increase the number of markers and gene regions associated with disease risk. Results need to be replicated to confirm association and functional studies, including differences in gene expression need to be conducted to identify the specific genes and pathways contributing to disease risk. Additional large studies should be undertaken in patients and controls with detailed phenotypic data and

biological samples to increase the power of genetic and functional studies. These studies will lead to better understanding of the biological basis of disease and more targets to help develop better diagnostic and therapeutic strategies.

Recommendation

Recruit new cohorts of endometriosis patients and controls with more detailed phenotypic information for genetic studies.

Recommendation

Conduct genomics research to understand gene expression in the endometrium of patients with endometriosis and controls.

Diet and nutrition play a major role in lifestyle changes that many women consider when confronted with endometriosis. Diet plausibly has a role in the etiology of endometriosis through effects at various levels including on steroid hormones; however, few published studies have examined diet and endometriosis risk,[52] resulting in no clear consensus recommendations. A recent study evaluated dietary risk factors for endometriosis in a population-based case–control study.[53] The results indicate that specific dietary components may be associated with endometriosis risk. Increased total fat consumption was associated with decreased endometriosis risk and increased β-carotene consumption and servings of fruit were associated with increased risk. There was also a suggestion of decreased endometriosis risk associated with the consumption of dairy products.

Recommendation

Research is needed to elucidate the role of diet in modifying the symptoms and underlying disease of endometriosis.

Endometriosis appears to be associated with some phenotypic variations likely attributable to the strong effect of the environment on the expression and function of genes influencing the traits. Novel clues on endometriosis pathogenesis may derive from the analysis of the phenotypic traits associated with the disease.[54] In a review of 11 studies on the association between endometriosis and body mass index (BMI) in the adult population and 5 studies on the same association during early life, a modest inverse correlation was found between endometriosis and adult BMI, and a stronger association was consistently demonstrated between endometriosis and early life body size, even after adjusting for confounding factors such as age, birth weight, age at menarche, parity, and oral contraceptive use. A second study has confirmed a lower BMI in patients with endometriosis than age- and smoking-status-matched controls, independent of confounding variables. Patients with the lowest BMI (<18.5) have been reported to be at a high risk of deep-infiltrating endometriosis.[55]

Recommendation

Studies be undertaken to investigate the relationship between phenotypic variables, including BMI and endometriosis.

There is strong evidence from nonhuman primate and rodent studies suggesting that environmental contaminants, specifically endocrine disrupting chemicals, may contribute to the pathogenesis of endometriosis. Timing of exposure appears to be important, as in utero exposure to the xenoestrogen diethylstilbesterol (DES) increases a woman's risk of developing endometriosis as an adult by 80% (relative risk [RR] = 1.8, confidence interval [CI]=1.2-2.8).[56] Animal studies also show that endometriosis can be promoted by adult exposures to organochlorines, a class of chemicals that includes the dioxin, tetrachlorodibenzo-p-dioxin, the pesticides methoxychlor and dichlorodiphenyltrichloroethane, and polychlorinated biphenyls with dioxin-like effects.[57] An equivocal literature exists regarding the relation between persistent organochlorine pollutants (POPs) and endometriosis in women, with differences attributed to methodologies. A recent study assessed the association between POPs and the odds of an endometriosis diagnosis and the consistency of findings by biological medium and study cohort.[58] Using a matched cohort design, it was shown that cohort-specific and biological-medium-specific POPs were associated with endometriosis, underscoring the importance of methodological considerations when interpreting findings.

Recommendation

Further research on the impact of environmental factors on endometriosis is warranted, with windows of susceptibility (including fetal, neonatal, childhood, and adolescent origins) being important criteria in the collection of information. Measurement of individual endocrine disrupting chemicals and environmental contaminants, timing of exposure, dose, and duration are important to determine, if known, and should be included in databases, where possible.

Pathophysiology

As identified at the WCE 2008 Research Directions Workshop,[1] one of the major challenges of working in endometriosis research is the need for a multidisciplinary approach. As a consequence, a wide range of disciplines and experimental approaches relevant to the study of endometriosis can be listed under the general heading of pathophysiology. These include, but are not limited to, physiology, pathology, immunology, and endocrinology, angiogenesis/vasculogenesis, stem cells, apoptosis, inflammation and pain, each of which can encompass approaches such as genomics, proteomics, and animal and in vitro models. The workshop did not attempt to develop a comprehensive set of recommendations topic by topic for each of these combinations, but rather to identify major themes and areas of importance.

Inflammation and Immunology

Endometriosis fulfills most of the classification criteria for autoimmune disease, including polyclonal B-cell activation,

immunological abnormalities in T- and B-cell functions, increased apoptosis, tissue damage, and multiorgan involvement.[59] Autoimmune diseases that may be associated with endometriosis include systemic lupus erythematosus (SLE), hypothyroidism, rheumatoid arthritis, Sjögren syndrome, and multiple sclerosis. The best evidence exists for an association with inflammatory bowel diseases. There is also a link between endometriosis and increased risk of allergic autoimmune disorders.[60]

Recommendation. The potential use of immunomodulators for treatment of endometriosis should be further investigated.

In contrast to other tissue sites, cyclical endometrial inflammation is physiological. However, dysregulation of this inflammatory response can lead to endometrial disorders, including endometriosis.[61] Local inflammation plays a role in pain and infertility associated with the disease, and may be extensively involved in molecular and cellular processes leading to development of endometriosis.[62] Human epithelial and stromal endometrial cells express nuclear factor-kappa B (NF-kB) proteins; NF-kB-mediated gene transcription promotes inflammation, invasion, angiogenesis, and cell proliferation and inhibits apoptosis of endometriotic cells.[63] Interleukin (IL)-6, IL-10, interferon (IFN), and transforming growth factor (TGF-β) are implicated in the immune and inflammatory responses in the pathogenesis of endometriosis.[61,64] However, evidence is mixed on the usefulness of anti-inflammatory agents to treat endometriosis symptoms, with a recent review concluding that there is no enough evidence to support the use of the anti-inflammatory pentoxifylline in the management of subfertility and relief of pain from endometriosis.[65] Conversely, it has been shown that lipoxin A4 and its receptor FPR2/ALX can regulate inflammatory events in the human endometrium and decidua of early pregnancy.[66] Mice treated with lipoxin A4, a lipid mediator that elicits anti-inflammatory and proresolution action, showed inhibited endometriotic lesion development with downregulated proinflammatory factors, suppressed activity of MMP9, and reduced vascular endothelial growth factor (VEGF) levels.[67]

Recommendation. The role of endogenous and exogenous anti-inflammatory mediators in the pathophysiology and treatment of endometriosis should be further investigated.

There is increasing evidence for marked changes in numbers and functions of leukocytes in the eutopic endometrium, peritoneal fluid, and in endometriotic lesions.[68] Peritoneal endometriosis is characterized by increased numbers of peritoneal macrophages and their secreted products.[69] The development of endometriotic implants in an immunocompetent mouse model is inhibited by retinoic acid. This effect may be caused, at least in part, by reduced IL-6 and MCP-1 production and enhanced differentiation of peritoneal macrophages.[70] The recruitment, possible proliferation, activation, and differentiation of monocytic lineage cells within the peritoneal cavity or within endometriosis lesions deserve further investigation.[69,71-73]

Recommendation. Research should be directed toward understanding the role of macrophages in endometriosis, and in particular how increased macrophage activation and reduced phagocytotic activity coexist in women with endometriosis.

The WES and the WERF investigators should develop/share research protocols for the study of macrophages in the context of endometriosis.

Oxidative Stress

Peritoneal oxidative stress is thought to be one of the major constituent of the endometriosis-associated inflammatory response. Excessive production of reactive oxygen species (ROS), secondary to peritoneal influx of prooxidants such as heme and iron, may induce cellular damage and increased proinflammatory gene expression through NF-kB activation. In particular, prostaglandin biosynthetic enzyme expression is regulated by this transcription factor, and increased peritoneal prostaglandin concentrations have been demonstrated in endometriosis.[74]

The ROS are proinflammatory mediators that modulate cell proliferation. The dysregulation of ROS production in endometriotic cells correlates with a proproliferative phenotype and may be implicated in the spreading of the disease.[75] Endometriotic cells display higher endogenous oxidative stress with an increase in ROS production, alterations in ROS detoxification pathways, and a drop in catalase levels. This increase in endogenous ROS correlated with increased cellular proliferation and activation of ERK1/2. These phenomena were abrogated by the antioxidant molecule N-acetyl-cysteine both in vitro and in a mouse model of endometriosis. These results suggest that antioxidant molecules could potentially be used as a treatment option for endometriosis.[75]

In a subsequent study by the same investigators, treatment of endometriotic cells with protein kinase inhibitors A771726, PD98059, or U0126 abrogated the phosphorylation of extracellular signal-regulated kinase (ERK) and significantly decreased cellular proliferation in vitro. In vivo A771726, leflunomide, PD98059, and U0126 modulated the growth of endometriotic implants in a mouse model of endometriosis.[76] Based on these results, it is suggested that protein kinase inhibitors could be considered as new candidates to treat endometriosis; however, further studies are needed to evaluate their effects and tolerability in humans.

Oxidative stress is implicated as a key factor in the pathogenesis of endometriosis. In a systematic review of oxidative stress biomarkers measured in patients with endometriosis, a total of 36 were identified. Of those 36 oxidative stress biomarkers, 23 were found to be significantly higher in patients with endometriosis compared to controls.[77]

Recommendation. A better understanding of the role of oxidative stress in the development and potential treatment of endometriosis is required.

Nerves, Neuropeptides, and Pain

Many clinicians and patients believe that endometriosis-associated pain is due to the lesions. Yet causality remains an enigma, because pain symptoms attributed to endometriosis occur in women without endometriosis and because pain symptoms and severity correlate poorly with lesion characteristics.[34]

The presence of nerve fibers in ectopic and more recently eutopic endometrial tissue has recently become a subject of major interest.[10,34,78-82] Several authors have reported the presence of nerve fibers in endometriotic lesions. Not surprisingly, ectopic and eutopic endometrium produce neurotrophic factors,[83] some of which are differentially expressed in cases of endometrioisis[84] and could serve as minimally invasive endometriosis biomarkers.[85] These observations have opened up a whole new field in the study of endometrial biology which may be critical for understanding mechanisms underlying the development, progression, variability and symptomatology of endometriosis.

The presence of unmyelinated sensory nerve fibers in the functional layer of endometrium and a significantly increased nerve fiber density in endometrium and myometrium in women with endometriosis suggests a possible role in pain perception. It has been reported that endometrial biopsy, with detection of nerve fibres, provides a reliability of diagnosis of endometriosis which is close to the accuracy of laparoscopic assessment by experienced gynecological laparoscopists.[86] Patients with endometriosis who have painful symptoms had more nerve fibers in peritoneal endometriotic lesions than patients with endometriosis who had no pain, and there is a correlation between pain score and the density of nerve fibers in peritoneal endometriotic lesions.[10,87] Regulatory peptides have been shown in endometrium. Corticotropin-releasing hormone and urocortin are expressed by endometriotic tissue and their deranged expression in endometrium of patients with endometriosis suggests that these neuropeptides may also participate in the pathogenesis of endometriosis.[88]

In a rat autotransplantation model of endometrium to the mesentery, vascularized endometriotic cysts become innervated with sensory and sympathetic fibers, and rats subsequently exhibit vaginal hyperalgesia.[81] Rudimentary sensory and sympathetic innervation appeared in the cysts at 2 weeks, sprouted further and more densely into the cyst wall by 4 weeks, and matured by 6 weeks posttransplant. Sensory fibers became abnormally functionally active between 2 and 3 weeks posttransplant, remaining active thereafter. Vaginal hyperalgesia became significant between 4 and 5 weeks posttransplant and stabilized after 6 to 8 weeks. Removing cysts before they acquired functional innervation prevented vaginal hyperalgesia from developing, whereas sham cyst removal did not. These findings suggest that painful endometriosis can be classified as a mixed inflammatory/neuropathic pain condition that opens new avenues for pain relief.[81]

In a rat model of autotransplantation of endometrium to the gastrocnemius muscle, cystic lesions developed within 2 weeks with stromal invasion of the muscle, nociceptor nerve fibers, and neuronal sprouting, and persistent mechanical hyperalgesia at the site of the lesions.[89] Intralesional, but not contralateral, injection of progesterone was dose-dependently antihyperalgesic as was systemic administration of leuprolide. This is the first model to record in vivo electrophysiological recordings from sensory neurons innervating the lesions which revealed a significantly increased response to sustained mechanical stimulation.[89] These results are consistent with clinical and pathological findings observed in patients with endometriosis, compatible with the ectopic endometrium as a source of pain.

In human studies, it has been reported that there is an imbalance between sympathetic and sensory nerve fibres in peritoneal endometriosis as well as an altered modulation of peritoneal fluids from patients with endometriosis on sympathetic and sensory innervation, which might directly be involved in the maintenance of inflammation and pain.[82]

Taken together, these reports show that endometriotic lesions can develop their own nerve supply, thereby creating a direct and 2-way interaction between lesions and the CNS.

Major advances in improving understanding of, and alleviating, pain in endometriosis will likely occur if the focus changes from lesions to pain. In turn, how endometriosis affects the CNS might better be examined in the context of mechanisms underlying other chronic pain conditions.[34]

Recommendation. Understanding the origins of the pain associated with endometriosis is a priority for endometriosis research; such work should include specialists in the pain field.

The development of suitable animal models for endometriosis-related pain research is a priority, including a nonhuman primate model and induced and spontaneous disease models.

It will be important to gain a better understanding of the function of nerve fibres in eutopic and ectopic endometrium from women with endometriosis.

There is a need to investigate whether meaningful pain phenotypes can be derived from patient data and can be related to patient outcomes of interest.

Angiogenesis and Lymphangiogenesis

Angiogenesis and lymphangiogenesis, or the development of new blood and lymphatic vessels from preexisting ones, are critical processes in the pathogenesis of endometriosis.

Several studies have investigated the potential for antiangiogenic treatment of endometriosis. Many substances have been shown to exert antiangiogenic effects on endometriotic lesions under experimental in vitro and in vivo conditions, including growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclooxygenase 2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator–activated receptor agonists, progestins, danazol, and gonadotropin-releasing hormone agonists.[90] However, clinical evidence for their efficacy in antiangiogenic endometriosis therapy is still lacking. Further

experimental studies, and in particular controlled clinical trials, are required to clarify whether antiangiogenic compounds can be effective in treating endometriosis without inducing severe side effects. Of major concern will be potential antiangiogenic effects in women seeking to become pregnant, where reduced blood vessel formation in the developing placenta and/or fetus could have catastrophic consequences.

Vasculogenesis is the de novo formation of microvessels from circulating endothelial progenitor cells. There is increasing evidence that vasculogenesis plays a role in blood vessel formation during growth of endometriotic lesions.[91,92] Whether vasculogenesis, as opposed to angiogenesis, provides an opportunity for the development of novel diagnostic and therapeutic strategies for endometriosis will require further investigation.

Recommendation. Further studies are required on the effectiveness and safety of antiangiogenic and antivasculogenic therapies for treating endometriosis.

A role for the pelvic lymphatic system in the spread of endometriosis has long been hypothesized, with this theory proposed by Halban early in the last century. However, relatively little is known specifically about lymphangiogenesis in endometriosis. Knowledge of lymphatic vessels and lymphangiogenesis in the uterus remained limited until the recent advent of specific markers for lymphatic endothelium.[93] It has recently been demonstrated that expression of the potent lymphangiogenic growth factors VEGF-C and VEGF-D and their receptors neuropilin 2 is dysregulated in the endometrium from women with endometriosis. Furthermore, significantly increased lymphatic microvessel density in women with endometriosis has been described in the endometrium during the proliferative phase,[94] and the presence of lymphatic vessels in and around peritoneal endometriotic lesions[95] and lymphangiogenesis in deep-infiltrating endometriotic lesions has been reported.[96] The lymphatic metastasis theory of endometriosis is supported by observations of the presence of endometriosis in pelvic lymph nodes and associations between deep-infiltrating endometriosis and lymph node involvement.[96-98] This indicates that in women with endometriosis, more endometrial stromal cells may reach or persist in uterine-draining lymph nodes, and immune function may be altered such that endometrial cells are less effectively contained and have greater opportunity for further transit and establishment of endometriotic lesions. Significantly increased presence of endometrial cells and altered immune environment has also been demonstrated in uterine-draining lymph nodes in the baboon model of induced endometriosis.[99]

Recommendation. It is important to better understand the contribution of endometrial and endometriotic lesion lymphangiogenesis to the development of endometriosis. This includes the study of uninvolved peritoneum from women with endometriosis and correlation of lymphangiogenic parameters with detailed information on symptoms, disease stage, lesion location and appearance, and response to treatment.

Ectopic endometriotic implants recruit their own neural and vascular supplies through neuroangiogenesis. The mechanisms and therapeutic implications of neuroangiogenesis in these lesions may lead to potential treatments for the control or elimination of endometriotic lesion growth and associated pain.[100]

Recommendation. Given the fundamental similarities that exist in the processes that lead to growth of vascular and neural tissues and the critical role that both of these play in endometriosis, there should be increased investigation into the mechanisms of neuroangiogenesis as they apply to endometriosis.

Stem Cells

Clonogenic cells and side populations have been identified in human endometrium; these cells are few in number and have the ability to give rise to a variety of differentiated cell types.[101,102] There is good evidence that adult progenitor stem cells contribute to the remarkable regenerative capacity of the endometrium.[103,104] It is also likely that these same progenitor stem cells have the capacity to generate endometriosis if shed in a retrograde fashion. Although progenitor stem cells reside in the uterus, mesenchymal stem cells may also travel from other tissues such as bone marrow to repopulate the progenitor population.[105,106] Currently, there are no definitive markers to allow isolation and characterization of endometrial progenitor or stem cells, and it is unknown what drives the recruitment and homing of these cells to eutopic endometrium or ectopic sites.[107,108] It is also possible that stem cells that are not of uterine origin may migrate to and cause or contribute to endometriotic lesions, both in the peritoneal cavity and in the rarer instances where endometriosis occurs outside of the peritoneal cavity.

Recommendation. Further research is required into all aspects of endometrial stem cell biology, including their role in initiating endometriosis, and whether inhibiting the recruitment of stem cells will limit the progression of endometriosis.

Apoptosis

Women with endometriosis are reported to have reduced endometrial apoptosis with increased expression of antiapoptotic and decreased expression of proapoptotic factors. It is thought that the decreased susceptibility of endometrial tissue to apoptosis may contribute to the pathogenesis of endometriosis.[109,110] Mitochondria have a pivotal role in apoptotic processes regulated by members of the B-cell lymphoma 2 (BCL-2) family. In the normal endometrium, BCL-2, acting as a cell death repressor, is reported to inhibit apoptosis during the proliferative phase of the cycle. Expression peaks in endometrial, glandular, and stromal cells in the proliferative phase. In endometriosis, there is altered expression of BCL-2 in the eutopic endometrium and thereby fewer apoptotic cells and abnormal survival in ectopic sites.[109] Few data report on expression of Fas in endometriotic tissues; in contrast, several

studies describe increased expression of Fas ligand. Endometrial BCL-2 expression may be stimulated by estrogen and downregulated by progesterone.[110]

A steroid receptor coactivator-1 (SRC-1)-null mouse model reveals that the mouse *SRC-1* gene has an essential role in endometriosis progression.[111] A 70-kDa SRC-1 proteolytic isoform is highly elevated both in the endometriotic tissue of mice with surgically induced endometriosis and in endometriotic stromal cells biopsied from patients with endometriosis compared to normal endometrium. In contrast to full-length SRC-1, the endometriotic 70-kDa SRC-1 C-terminal fragment prevents TNF-α-mediated apoptosis in human endometrial epithelial cells and causes the epithelial–mesenchymal transition and the invasion of human endometrial cells that are hallmarks of progressive endometriosis. The newly identified SRC-1 isoform functional axis promotes pathogenic progression of endometriosis.[111]

Recommendation. Further work is required to determine whether manipulation of the apoptotic pathway can be harnessed as a therapeutic strategy for endometriosis.

Endometriosis-Related MicroRNAs Work

MicroRNAs (miRNAs) are short, single-stranded RNAs that regulate gene expression at the posttranscriptional level. A systematic review of the literature was recently undertaken to determine (1) the expression and functions of miRNAs in mammalian female reproductive tissues with a focus on endometriosis and the malignancies and fertility disorders related to this disease and (2) the potential roles played by validated mRNA targets of endometriosis-associated miRNAs.[112] The authors conclude that miRNAs may play an important role in endometriotic lesion development, including regulatory functions associated with hypoxia, inflammation, tissue repair, TGF-β-regulated pathways, cell growth, cell proliferation, apoptosis, extracellular matrix remodeling, and angiogenesis.

In a study aimed at understanding the role of miRNAs in the pathogenesis of endometriomas, a transcriptome-microRNAome analysis of endometriomas and eutopic endometrium using next-generation sequencing technology was undertaken.[113] The authors concluded that miRNA appears to play important roles in the pathophysiology of uterine function and dysfunction, including endometriosis. Other workers have shown that expression levels of miRNAs related to angiogenesis were different in eutopic endometrium from that observed in ovarian endometrioma. They conclude that this could influence the expression of angiogenic factors and play a role in the pathogenesis of endometriosis.[114]

Recommendation. More work on the role of miRNAs is required, including using miRNAs as biomarkers and therapeutic tools for endometriosis

Animal and Other Preclinical Models

The cornerstone of developing new therapies for endometriosis is the confidence and translational value placed in the preclinical models used to assess efficacy of emerging approaches.[115] In a systematic review of preclinical efficacy data from rodent and nonhuman primates between 2000 and 2010, 94 publications were identified which met the criteria for review. Efficacy studies had been conducted in a wide range of different models with no clear consensus on which model or end point had the most translational value. The authors concluded that greater scrutiny of the preclinical efficacy of models, end points, and experimental designs are needed if the desire of translating novel treatment approaches is to be realized in women with endometriosis.[115]

Recommendation. Appropriate animal and in vitro models for preclinical studies of endometriosis therapies should be agreed upon by the endometriosis research community.

Use of Targeted Transgenic Models

It is becoming increasingly evident that altered expression of genes in a pathological context contributes to many of the biological processes that are dysregulated in endometriosis, including cell proliferation, inhibition of apoptosis, and altered hormonal sensitivity. Thus, studies focused on gene regulation using transgenic models will provide valuable insights into mechanisms that may contribute to endometriosis.[116,117,111]

Recommendation. Targeted gene knockout and transgenic models should be employed to investigate the function of genes in the context of endometriosis.

Progestins and Endometriosis

Progestins have overall anti-inflammatory activity, and there appears to be progesterone resistance in endometriotic lesions and eutopic endometrium of women with endometriosis. Given that different progestins have different glucocorticoid and androgenic activity there may be opportunities for modifying treatments to improve outcomes. Selective progesterone receptor modulators (SPRMs) may also have a role in treating endometriosis, although evidence to support this is lacking to date.

Recommendation. To continue clinical and basic studies to determine the effectiveness of different progestins and SPRMs as agents for treating endometriosis as well as studies aimed at understanding progesterone resistance in eutopic and ectopic endometrium.

Role of the Ovary as a Target of Endometriosis

Endometriosis and ovarian cancer have been linked by a number of studies. Most recently, in a study of 13 226 controls and 7911 women with invasive ovarian cancer, self-reported endometriosis was associated with a significantly increased risk of

clear-cell, low-grade serous, and endometrioid invasive ovarian cancers. No association was noted between endometriosis and risk of mucinous or high-grade serous invasive ovarian cancer or borderline tumors of either subtype.[118]

Recommendation. Future research should consider the ovary as a target of endometriosis.

Role of the Microbiome in Endometriosis

Clinical assessment of women with pelvic pain can be a poor indicator of disease seen at laparoscopy.[119] In a study of pelvic inflammatory disease in 109 women, 22 at laparoscopy had salpingitis, 19 had adhesions without salpingitis, 20 had endometriosis or ovarian pathology, and 48 no observable abnormality. In all laparoscopic categories, Ureaplasma spp and *Mycoplasma hominis*, but not *Mycoplasma genitalium*, were at least as common in the cervix/vagina as *Chlamydia trachomatis* and equally frequent in the endometrium. The results reported for the whole group of women with pain highlight the difficulties in making a precise microbial diagnosis and highlight the need for further investigation into the links between the microbiome, pain, and endometriosis.

Recommendation. Metagenomic studies should be undertaken of the microbiome of the reproductive tract and/or the gut in women with or without endometriosis.

A number of important recommendations remain essentially unchanged from the 2008 Research Directions Workshop.[1] These include:

Heterogeneity of endometriosis lesions should be investigated using the full range of pathological and analytical approaches to ascertain whether an association exists between different lesion types and any given symptomatology.

Recommendation. A better understanding of the role of eutopic endometrium in the establishment and continuation of endometriosis is required.

Research should be performed on menstrual tissue, including material obtained from the peritoneal cavity by laparoscopy performed at the time of menstruation. Differences in retrogradely shed menstrual material between women with and without endometriosis should be defined, including but not limited to soluble mediators, endometrial cells and leucocytes.

More research is needed in order to better understand the biology and function of macroscopically normal peritoneum in women with and without endometriosis.

A better understanding of the mechanisms that underlie fibrosis and adhesion formation in the peritoneal cavity of women with endometriosis is required.

Research Policy

Throughout the 2011 WCE Research Directions Workshop, a number of recommendations and suggestions were made that related more to research policy than specific research directions. Many of these issues were recognized as being of major importance to ongoing progress in endometriosis research, and hence these have been grouped under a series of headings at the end of this document.

Data Registries and Biobanks

There is significant cost and expertise associated with collecting accurate and detailed clinical histories, adequate numbers of well-characterized endometrial biopsies and endometriotic lesions, peripheral blood samples, and other tissue specimens required for endometriosis research. Such samples have the greatest value when collected using systematic protocols and accompanied by detailed clinical classification of the patients.

Recommendation. That networks and/or biobanks and databases replete with patient clinical data are established to increase sample availability and improve study power for endometriosis research, including assessment and validation of biomarkers. Standard operating procedures (SOPs) should be established for tissue acquisition, processing, storage, and distribution. These activities should take account of existing databases and resources regarding patients with endometriosis.

The WERF should define guiding principles for establishing a global registry for endometriosis biobanks and databanks and take the lead in identifying SOPs, a consensus on clinically relevant questions and promote standardized definitions, prospective documentation and pragmatic-oriented research designs.

Data from genetic and gene expression studies should be submitted to online repositories like gene ontology (GO) and microarray express in a standard format suitable for sharing (and use in meta analyses).

A simplified questionnaire for assessment of QoL and pain outcomes is required.

The ultimate goal will be to integtrate voluminous available database and new data with comprehensive enodmetriosis patient/cellular/genetic phenotypes to elucidate disease phenotypes, pathogenesis, and pathophysiology for eventual preventive as well as targeted therapeutic strategies. Expertise of physicians and other health care providers, patients, epidemiologists, biostatisticians/ bioinformaticians, geneticists, immunologists, toxicologists, endometriosis researchers, pain and infectious disease specialists, and electronic medical record data are recommended.

The WERF creates a global ''endometriosis phenome'' with extensive and standardized annotation of patients' medical, surgical, family, social, and exposure histories and current and evolving multidemnsional knowledge networks of cellular and genetic/ epigenetic proteomic, metabolomic systems for a new ''taxonomy of endometriosis disease.''

Centers of Expertise

Endometriosis researchers and clinicians in some countries have moved to establishing ''centres of expertise.'' Although Centers of Expertise create the potential for significant

advances in specialist care, research, and outcomes of patients with endometriosis, there currently exists some debate over exactly what the definition of such a center should be. Among quality outcomes that should be considered is patient centeredness of endometriosis care.[120]

Recommendation. There should be a definition of what an endometriosis center of expertise is, based on quantifiable measures that are process and structure related, with quality indicators that are outcome related.

Multidisciplinary Approaches

One of the major issues identified at both the 2008 and the 2011 WCE Research Directions Workshops was the need for multidisciplinary expertise in developing and prosecuting endometriosis-related research projects, in conjunction with sufficient funding to allow meaningful projects to be undertaken.

Recommendation. There is a need for a multidisciplinary approach to research in all aspects of endometriosis, to include reproductive medicine physicians, reproductive surgeons, biologists, pathologists, oncologists, epidemiologists, geneticists, immunologists, toxicologists, pain specialists, infectious disease specialists, biostatisticians, bioinformaticians, and others to enable effective, accurate, and timely diagnosis, determination of those at risk, and prevention and treatment of endometriosis and associated disorders.

The WES should look to educate, interact with, and involve other specialists with the purpose of gaining a better understanding of the disease, with a strong focus on translating research outcomes into better treatment and improved QoL for women with endometriosis.

Large surgical centers should participate in basic research networks, and efforts should be made to maximize the amount of data that are generated from clinical trials through add-on studies and collaboration with other relevant disciplines.

Guidelines and Implementation

Recommendation. There should be a triannual workshop of research directions in endometriosis based on a consensus approach lead by the WES and the WERF and based on best-available scientific evidence.

Recommendation. The WES and the WERF should formulate various task forces as required to move forward recommendations from this meeting.

Lobbying and Endometriosis Organizations

Endometriosis Organizations, which are often led by women with endometriosis, have the ability to raise public awareness about the challenges posed by endometriosis more effectively than scientists or physicians, not the least because they are seen by politicians and the general public to have greater credibility. This gives greater access to media and better effectiveness for educational campaigns. Different endometriosis organizations have been responsible for multimillion dollar outreach campaigns, public service announcement campaigns, numerous outreach mailings, and e-mail blitzes to key stakeholders, educational outreach videos, books, and brochures. This has contributed significantly to raising the profile of endometriosis as a disease. Women with endometriosis often have more persuasive power with government bodies, politicians, and institutions. Personal stories and sharing experience and impact of a disease are more powerful than simply asking for research funds, and women with endometriosis have more political capital as they can represent a significant block of votes.

Recommendation. Women with endometriosis should be included in meetings and focus groups to develop new insights and approaches into research.

Endometriosis researchers should engage women with endometriosis and the wider community with activities that include sharing and communicating research results.

Endometriosis researchers and women with endometriosis should work together to optimize funding support for endometriosis research.

Discussion

This research directions consensus statement builds on earlier efforts to develop a research priorities consensus statement for endometriosis.[1] Although by no means proscriptive, the recommendations contained within provide important guidance on many of the key issues confronting researchers in the field. One of the emerging requirements to facilitate research is better organization of ideas and resources. This is reflected in the 6 separate recommendations that seek organizational input from the WES and/or the WERF to establish groups or taskforces to address-specific issues. Another new area addressed in these recommendations is the section on research policy. Critical issues that facilitate good research include biobanks and data registries, multidisciplinary approaches, and guidelines. Equally important is the inclusion of patient groups in all steps of the research process, from generation of research ideas through lobbying, fund-raising, and dissemination of results.

Within the main body of recommendations, some areas of research appear to have progressed more rapidly than others since the last research directions workshop in 2008.[1] In particular, some of the advances in genetics and associated technologies have moved the field forward significantly over the past 3 years.[8,9] These studies provide important leads for many different researchers in the field and will hopefully open a number of new doors that will eventually lead to improved diagnostics and therapeutics for endometriosis.

One area of research need that was repeatedly highlighted at the 2011 meeting was work on all aspects of pain.[34] The meeting recognized the impact that pain has on many women with endometriosis and attached significant priority to the need for

research on all aspects of pain, including basic mechanisms, classification, and treatment.

It is the hope of the workshop organizers and participants that this international consensus document will be a useful tool in aiding researchers to develop new interdisciplinary research proposals and obtain increased funding support from multiple disciplines for work on endometriosis. This research priorities consensus statement will have a limited life and a revised and updated set of research priorities which builds on this document, and progress as a result of our efforts, will be developed in conjunction with the 12th World Congress on Endometriosis to be held from April 30, 2014, to May 3, 2014, in São Paulo, Brazil.

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