Reproductive Sciences
1-25

DOI: 10.1177/1933719116654991
rs.sagepub.com
SAGE

Research Priorities for Endometriosis: Recommendations From a Global Consortium of Investigators in Endometriosis

Peter A. W. Rogers, BSc, PhD[1], G. David Adamson, MD[2,3], Moamar Al-Jefout, MD, PhD[4], Christian M. Becker, MD[5], Thomas M. D'Hooghe, MD, PhD[6], Gerard A. J. Dunselman, MD, PhD[7], Asgerally Fazleabas, PhD[8], Linda C. Giudice, MD, PhD[3,9,10], Andrew W. Horne, MBChB, PhD[11], M. Louise Hull, BSc, MBChB, PhD[12], Lone Hummelshoj[3,10], Stacey A. Missmer, ScD[3,13], Grant W. Montgomery, PhD[14], Pamela Stratton, MD[15], Robert N. Taylor, MD, PhD[10,16], Luk Rombauts, MD, PhD[3,10,17], Philippa T. Saunders, PhD[18], Katy Vincent, MRCOG, DPhil[5], Krina T. Zondervan, DPhil[5,19], and for the WES/WERF Consortium for Research Priorities in Endometriosis

Abstract

The 3rd International Consensus Workshop on Research Priorities in Endometriosis was held in São Paulo on May 4, 2014, following the 12th World Congress on Endometriosis. The workshop was attended by 60 participants from 19 countries and was divided into 5 main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management, and research policy. This research priorities consensus statement builds on earlier efforts to develop research directions for endometriosis. Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 41 remained unchanged, 13 were updated, and 2 were deemed to be completed. Fifty-three new research recommendations were made at the 2014 meeting in Sao Paulo, which in addition to the 13 updated recommendations resulted in a total of 66 new recommendations for research. The research recommendations published herein, as well as those from the 2 previous papers from international consensus workshops, are an attempt to promote high-quality research in endometriosis by identifying and

[1] University of Melbourne, Melbourne, Australia
[2] Palo Alto Medical Foundation Fertility Physicians of Northern California, Palo Alto, CA, USA
[3] World Endometriosis Research Foundation (WERF), London, United Kingdom
[4] Mutah University, Maw'tah, Jordan
[5] Nuffield Department of Obstetrics & Gynaecology, Endometriosis Care Centre, Oxford, United Kingdom
[6] University of Leuven (KU Leuven), Leuven, Belgium
[7] Department of Obstetrics & Gynaecology, Research Institute GROW, Maastricht University Medical Centre, Maastricht, the Netherlands
[8] Michigan State University, Michigan, MI, USA
[9] University of California, San Francisco, CA, USA
[10] World Endometriosis Society (WES), Vancouver, Canada
[11] MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom
[12] The Robinson Institute, University of Adelaide, Adelaide, Australia
[13] Harvard Schools of Medicine and Public Health, Boston, MA, USA
[14] QIMR Berghofer Medical Research Institute, Brisbane, Australia
[15] NIH, Bethesda, MD, USA
[16] Wake Forest School of Medicine, Winston-Salem, NC, USA
[17] Monash University, Clayton, Australia
[18] MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom
[19] Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom

Corresponding Author:
Peter A. W. Rogers, Department of Obstetrics & Gynaecology, Royal Women's Hospital, University of Melbourne, Level 7, 20 Flemington Rd, Parkville, Victoria 3052, Australia.
Email: parogers@unimelb.edu.au

agreeing on key issues that require investigation. New areas included in the 2014 recommendations include infertility, patient stratification, and research in emerging nations, in addition to an increased focus on translational research. A revised and updated set of research priorities that builds on this document will be developed at the 13th World Congress on Endometriosis to be held on May 17–20, 2017, in Vancouver, British Columbia, Canada.

Keywords
endometriosis, research priorities, international workshop, consensus report

Introduction

The 3rd International Consensus Workshop on Research Directions in Endometriosis was held in São Paulo on May 4, 2014, the day following the 12th World Congress on Endometriosis (WCE). The workshop was supported by the World Endometriosis Society (WES) and the World Endometriosis Research Foundation (WERF). Previous research directions workshops have been held in conjunction with earlier WCE meetings in Melbourne in 2008 and Montpellier in 2011, both resulting in the publication of a number of research recommendations.[1,2]

The São Paulo workshop, attended by 60 participants from 19 countries, was divided into 5 main sessions covering pathogenesis/pathophysiology, symptoms, diagnosis/classification/prognosis, disease/symptom management, and research policy. Within each session, speakers provided updates on areas of significant research progress in the past 3 years, followed by suggestions for new research directions. On each topic, discussion was opened to all workshop participants and new research recommendations were developed. Following the workshop, each speaker was asked to scrutinize a transcript of the meeting and using the 56 research recommendations from 2011 as a starting point (1) to list recommendations that are still relevant and should remain unchanged (ie, do not need updating), (2) to identify recommendations that are no longer relevant (ie, have been completed or superseded), and (3) from the transcript of the meeting, list new or updated recommendations that were suggested at the workshop. This paper records the new and updated recommendations from the workshop. The status of recommendations from 2011[2] is provided in Table 1.

To broaden thinking and generate new ideas, speakers were also asked to consider 3 new themes across all of the sessions: (1) novel concepts or approaches that endometriosis researchers can emulate from research successes in other complex diseases, (2) enhancing research in emerging regions, and (3) prioritization of translational research: Where should we be focusing our research efforts? Where relevant, these themes are incorporated into this report. In addition, compared to the 2011 meeting, the workshop included an enhanced focus on symptoms of endometriosis, with sessions on pain, infertility, and the patients' perspective.

Of the 56 research recommendations from the 2011 meeting in Montpellier, a total of 44 remained unchanged, 8 were updated, and only 4 were deemed to be no longer relevant, with 2 superseded and 2 completed. Fifty-three new research recommendations were made at the 2014 meeting in Sao Paulo, which in addition to the 13 updated recommendations gives a total of 66. These are listed below.

Background

Endometriosis is a common and costly disorder affecting 6% to 10% of reproductive-age women[5] and the most common cause of chronic pelvic pain (CPP).[6] The financial burden of endometriosis on the health-care system is substantial, with the direct and indirect annual costs of endometriosis estimated at US$12 419/woman affected (~€9579).[7] The same authors reported decreased quality of life as the most important predictor of direct health-care and total costs. The economic burden associated with endometriosis is similar to other chronic diseases such as diabetes, Crohn disease, and rheumatoid arthritis.[7]

There is a delay of up to 9 years between symptom onset and definitive diagnosis of endometriosis, depending on health-care settings.[8,9] It has been estimated that affected women lose, on average, 10.8 hours of work weekly, mainly owing to reduced effectiveness while working. Loss of work productivity translates into significant costs, ranging from US$208 in Nigeria to US$23 712 in Italy per woman/year.[8] There is currently no known cure for endometriosis. Following surgical management, symptomatic recurrence ranges from 20% to 40% and many women require additional surgery at a later time.[10]

The research recommendations published in this report, as well as those from the 2 previous papers from international consensus workshops, are aimed at promoting high-quality research into endometriosis by identifying and agreeing on the key issues that require investigation. Although the recommendations are offered as a guide only, it is notable that the 2009 and 2013 papers have been cited 79 and 27 times, respectively (Web of Science data September 2015) by other publications, suggesting that they have been of considerable use to the endometriosis research community. Significant research effort is occurring into all aspects of endometriosis: between the 2011 and 2014 WCE meetings, a total of 2524 new scientific publications on endometriosis were recorded on PubMed. Despite this research activity, and somewhat disappointingly, only 2 of the 56 recommendations from the 2011 Research Directions Workshop were deemed to have been satisfactorily addressed.

One key area of progress since the 2011 meeting has been made in research policy. To encourage and facilitate the required large, international collaborations, the WERF launched the Endometriosis Phenome and Biobanking

Table 1. Recommendations Formulated at the 2008[1] and 2011[2] Workshops, with an Indication in "Status" on Whether These Were Updated at the 2014 Workshop and to What Extent Progress Has Been Made.

		Status
Diagnosis		
1	Discovery and identification of new and validation of existing endometriosis-associated biomarkers is required to develop an accurate, noninvasive method to diagnose endometriosis.	Recommendation updated in 2014.
2	The different clinical classifications of endometriosis need to be taken into consideration as part of the evaluation of predictive and diagnostic biomarkers.	WES-led consensus workshop held on April 30, 2014 to commence this process.
3	Advances in imaging techniques should be monitored for application to diagnosis of endometriosis.	Recommendation updated in 2014.
Classification and progress		
4	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.	WERF has developed tools (EPHect) and made these freely available to allow for consistent data collection across centers worldwide.[3,4]
5	WES and 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), intraoperative, and biochemical findings.	This will be an outcome of WERF EPHect once sufficient data have been collected.
Clinical trials, treatment, and outcomes		
6	Center randomized controlled trials and long-term follow-up studies comparing different endometriosis treatment options against defined outcome measures.	Recommendation updated in 2014.
7	Clinical trials in endometriosis should focus on outcomes of high relevance to women, ie, quality of life and key fertility outcomes including live births.	
8	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.	
9	Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including inflammatory nociceptive, neuropathic, and central pain.	Recommendation updated in 2014.
10	Novel medical treatments for endometriosis should be investigated.	Recommendation updated in 2014.
11	Investigate the link between dysmenorrhea and endometriosis and early intervention strategies in younger women.	
12	Studies on pregnancy and pregnancy outcomes in women with endometriosis need to be undertaken.	Recommendation updated in 2014.
Epidemiology		
13	Recruit new cohorts of patients with endometriosis and controls with more detailed phenotypic information for genetic studies.	
14	Conduct genomics research to understand gene expression in the endometrium of patients with endometriosis and controls.	
15	Research is needed to elucidate the role of diet in modifying the symptoms and underlying disease of endometriosis.	Recommendation updated in 2014.
16	Studies be undertaken to investigate the relationship between phenotypic variables, including BMI and endometriosis.	
17	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		
Inflammation and immunology		
18	The potential use of immunomodulators for treatment of endometriosis should be investigated.	
19	The role of endogenous and exogenous anti-inflammatory mediators in the pathophysiology and treatment of endometriosis should be further investigated.	
20	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.	Recommendation updated in 2014.
21	WES and WERF investigators should develop/share research protocols for the study of macrophages in the context of endometriosis.	

(continued)

Table 1. (continued)

		Status
	Oxidative stress	
22	A better understanding of the role of oxidative stress in the development and potential treatment of endometriosis is required.	
	Nerves, neuropeptides, and pain	
23	Understanding the origins of the pain associated with endometriosis is a priority for endometriosis research: such work should include specialists in the pain field.	
24	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.	
25	It will be important to gain a better understanding of the function of nerve fibers in eutopic and ectopic endometrium from women with endometriosis.	
26	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.	Recommendation updated in 2014.
	Angiogenesis and lymphangiogenesis	
27	Further studies are required on the effectiveness and safety of antiangiogenic and antivasculogenic therapies for treating endometriosis.	
28	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.	
29	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	
30	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.	Recommendation updated in 2014.
	Apoptosis	
31	Further work is required to determine whether manipulation of the apoptotic pathway can be harnessed as a therapeutic strategy for endometriosis.	
	Endometriosis-related miRNA work	
32	More work on the role of miRNAs is required, including using miRNAs as biomarkers and therapeutic tools for endometriosis	
	Animal and other preclinical models	
33	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	
34	Targeted gene knockout and transgenic models should be used to investigate the function of genes in the context of endometriosis.	
	Progestins and endometriosis	
35	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	
36	Future research should consider the ovary as a target of endometriosis.	
	Role of the microbiome in endometriosis	
37	Metagenomic studies should be undertaken of the microbiome of the reproductive tract and/or the gut in women with or without endometriosis.	
	Unchanged recommendations from 2008[1]	
38	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.	
39	A better understanding of the role of eutopic endometrium in the establishment and continuation of endometriosis is required.	
40	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.	

(continued)

Table 1. (continued)

		Status
41	More research is needed in order to better understand the biology and function of macroscopically normal peritoneum in women with and without endometriosis.	Recommendation updated in 2014.
42	A better understanding of the mechanisms that underlie fibrosis and adhesion formation in the peritoneal cavity of women with endometriosis is required.	
Research policy		
Data registries and biobanks		
43	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.	Complete. WERF EPHect tools address this: http://endometriosisfoundation.org/ephect/.
44	WERF should define guiding principles for establishing a global registry for endometriosis biobanks and databanks and take the lead in identifying SOP's, a consensus on clinically relevant questions and promote standardized definitions, prospective documentation, and pragmatic oriented research designs.	Complete. WERF EPHect tools address this: http://endometriosisfoundation.org/ephect/.
45	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).	
46	A simplified questionnaire for assessment of quality of life and pain outcomes is required.	Recommendation updated in 2014.
47	WERF create a global "endometriosis phenome" with extensive and standardized annotation of patients' medical, surgical, family, social, and exposure histories, and current and evolving multidimensional knowledge networks of cellular and genetic/epigenetic proteomic, metabolomic systems for a new "taxonomy of endometriosis disease"	
Centers of expertise		
48	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		
49	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.	
50	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 quality of life for women with endometriosis.	
51	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		
52	There should be a triannual workshop of research directions in endometriosis based on a consensus approach lead by WES and WERF and based on best available scientific evidence.	Triannual workshops have been held in March 2008, September 2011, and May 2014. The next workshop is scheduled for May 21, 2017.
53	WES and WERF should formulate various task forces as required to move forward recommendations from this meeting.	
Lobbying and endometriosis organizations		
54	Women with endometriosis should be included in meetings and focus groups to develop new insights and approaches to research.	Recommendation updated in 2014. Women with endometriosis are invited to participate in WES and WERF meetings.
55	Endometriosis researchers should engage women with endometriosis and the wider community with activities that include sharing and communicating research results.	
56	Endometriosis researchers and women with endometriosis should work together to optimize funding support for endometriosis research.	

Abbreviations: BMI, body mass index; EPHect, Endometriosis Phenome and Biobanking Harmonisation Project; SPRMs, Selective Progesterone Receptor Modulators; WERF, World Endometriosis Research Foundation; WES, World Endometriosis Society.

Harmonisation Project (EPHect; http://endometriosisfoundation.org/ephect/) led by Stacey Missmer of Harvard University and Krina Zondervan from the University of Oxford.[3,4,11,12] The WERF EPHect team includes 34 experts from 16 countries as well as 3 industry sponsors—many of whom were present at the WES/WERF Research Workshop. Together, this group developed and published freely available clinical and surgical data collection tools along with protocols to standardize collection of biological samples to support discovery and innovation. To maximize collaborative opportunity, there is a facility for centers that use the WERF EPHect tools and protocols to identify themselves on the website above.

Pathogenesis and Pathophysiology

Epidemiology

The consensus meeting approached epidemiology from its 2 definitions: first, as the discipline focused upon determining who is at risk for endometriosis (which of a girl or woman's characteristics or exposures are associated with her developing endometriosis) and how those characteristics and exposures cause or impact endometriosis pathogenesis and pathophysiology; second, as the science underlying the methods by which valid human studies must be conducted. It matters who we choose to sample from among the population of girls and women and who we compare to whom for our studies of pathogenesis and pathophysiology. The broad consensus was that future studies need to be large and diverse to quantify and evaluate with adequate statistical power the importance or insignificance of the diversity of disease presentation, whether it be in macroscopic subtypes (superficial peritoneal, ovarian, and deep infiltrating endometriosis; propensity for scarring and adhesions), symptom presentation (dysmenorrhea, acyclic pelvic pain, dyspareunia, infertility), and treatment response.

Two topics summarize the new recommendations: (1) a need for our field to thoughtfully and actively determine what data are needed to quantify endometriosis disease burden and to facilitate discovery that takes into account phenotypic variation and (2) endometriosis must be addressed and consistent data must be collected for research and clinical needs across the life course, in adolescence, pregnancy, and throughout adulthood. Adolescents in particular are an underserved group with high morbidity and social impact, and yet this age is likely the critical window for disease etiologic discovery and intervention.[13]

Endometriosis macroscopically appears and behaves differently among patients. However, what patterns and differences are important to target for etiologic discovery, treatment development, and ultimately cure—and perhaps prevention—remain unclear. Scientific progress has been limited in part due to small studies and geographic restrictions that make identification of these unique disease groups impossible.

There were no recommendations from the 2011 meeting that are no longer relevant; 2 remain current.

Since the 2011 World Congress to this 2014 consensus meeting, only 2 epidemiological study papers evaluated outcomes comparing and contrasting subtypes of macrodisease presentation of endometriosis. One included superficial peritoneal, ovarian, and deep infiltrating categories.[14] The other applied the American Society for Reproductive Medicine (ASRM) classification system and the Endometriosis Fertility Index (EFI).[15] There was nothing published comparing patients by categories of symptomatology or peritoneal lesion types. There were many publications with "stage" as a keyword; however, none published prior to the workshop evaluated stage by comparing the study outcomes among cases stratified by stage. One subsequent paper found a weak correlation between stage of endometriosis and age, concluding that minimal or mild endometriosis is equally likely to be present in women of all ages and that endometriosis in its severe form is not age dependent.[16]

Regarding diet, there were 7 studies published during this 3-year time period; they included focus on micronutrients, a gluten-free diet, fish oil, flavonoids, and systemic antioxidant capacity. There were a rich range of methods and expertise: animal models, small human trials, and cohort studies.[17-23] Among the 3 animal studies, the one using a Wistar albino rat model observed that dose-dependent vitamin C supplementation significantly reduced the volumes and weights of the endometriotic cysts.[18] In a chimeric mouse model, dietary fish oil supplementation inhibited formation of endometriosis-associated adhesions,[21] whereas in a BALB/c mouse model, xanthohumol was observed to inhibit the development of endometriotic lesions without evidence of a negative impact on the uterine horn or ovaries.[22] The human studies included a small case ($n = 25$)–control ($n = 20$) study, which reported a higher current intake of fiber among the women with endometriosis and a higher polyunsaturated fat intake among the controls.[23] Also, a cohort of $\sim$150 women reporting endometriosis-associated pain were asked to commit to a gluten-free diet for 12 months. At the end of follow-up, a significant majority reported a decrease in pain and improved physical and social functioning in unadjusted analyses.[17] The largest studies ($n \sim 100\,000$ participants with follow-up duration of >15 years) published from the Nurses' Health Study 2 cohort reported a significantly decreased risk of endometriosis among women who consumed larger quantities of dairy foods rich in vitamin D, calcium, or magnesium.[19] They also observed a decreased risk with greater vitamin B and C intake, but from food sources, not from supplements.[20]

Two body mass index (BMI) studies reinforced the robustly observed higher prevalence of endometriosis among lean women.[24,25] Overall, those with lean BMI at age 18 (<18.5 kg/m^2) had 20% to 25% greater risk of endometriosis compared to women with normal BMI (18.5-24.9 kg/m^2), 40% greater than overweight women, and nearly double the risk of morbidly obese women (P value, test for linear trend <.0001).

Finally, with respect to environmental toxicants, only 3 studies were published between the 2011 and 2014 World Congresses.[26-28] The study of environmental toxicant risk factors was the only topic that included data evaluating the importance of age at exposure, with studies that included in utero exposure, childhood exposure, and exposure during adulthood. Earlier

life exposures to toxicants may be the critical window for impacting initiation or promotion of endometriosis development, whereas later life exposures may impact symptom severity or treatment resistance. Within the French Teachers' Cohort that included ~75 000 women, Kvaskoff and colleagues observed a modest but significant increased risk of endometriosis among women who had had pets as a child or lived on a farm with livestock and a larger increased risk (up to 34%) for those who were exposed to passive cigarette smoke.[28] The Women's Risk of Endometriosis case–control study based in the US Pacific Northwest observed significantly higher serum concentrations of the persistent organochlorine pesticides β-hexachlorocyclohexane and mirex among case women compared to control women.[26] However, within the Endometriosis, Natural History, Disease, Outcome Study, the matched cohort analyses suggested no association between risk of endometriosis and exposure in utero with maternal or paternal smoking or with maternal consumption of alcohol, caffeine, or vitamins.[27]

New Recommendations

1. *Recommendation (new):* Facilitate and prioritize collection of country-/region-specific endometriosis prevalence data to facilitate calculation of disease burden statistics. This is particularly critical in emerging regions.
2. *Recommendation (new):* Document the social impact of endometriosis using standardized instruments. This is particularly critical for inclusion of adolescents.
3. *Recommendation (new):* Devise standardized questions, or tools, for participant query and medical record abstraction of endometriosis and endometriosis-related symptom data that could validly facilitate adding these data to many large ongoing international cohorts.

Genetics, Epigenetics, and Genomics

Genetic and environmental factors contribute to endometriosis risk, and the disease is inherited as a complex trait.[29,30] Substantial progress has been made in the discovery of genomic regions contributing to endometriosis risk. New genome-wide association (GWA) studies,[31] replication studies,[32,33] and meta-analyses[30,34] show remarkable consistency in the size and direction of effect for risk variants across studies and across ethnic groups. There are at least 6 genomic regions showing significant association with endometriosis of any disease stage.[30] In addition, association between markers near the interleukin 1A gene first reported in Japanese patients was confirmed recently.[35,36] There is genetic overlap between endometriosis and both waste–hip ratio[37] and ovarian cancer,[38] and understanding the relationships between endometriosis and other reproductive traits will be one important direction for future studies as large data sets become available.

The combined data show the genetic contribution to endometriosis results from a large number of variants of small effect. Results from the estimated contributions of the known genomic regions[30,31,34] and the single-nucleotide polymorphism (SNP) heritability[39] suggest many more variants remain to be identified. Knowing and understanding the effects of these variants will aid understanding of disease origin and progression and the identification of biomarkers for disease as well as novel drug targets. To this end, genotyping is being completed in additional case–control samples to conduct new GWA studies and combine results in a large new meta-analysis that will increase the sample size to at least 17 000 cases. This sample size increase will increase power for gene discovery but is still modest compared with current projects of 50 000 to 100 000 cases in other diseases. In addition, an important objective for future studies is to use genetic approaches to help understand the similarities and differences between different subtypes of endometriosis including peritoneal disease, ovarian endometriomas, and deep infiltrating disease. Most of the large samples used for GWA studies lack detailed information on disease subtypes, and there is an important need for new large studies where detailed phenotypic data, medical records, and genotype data are available for combined epidemiological and genetic studies.[40]

There were no recommendations from the 2011 meeting that are no longer relevant; 2 recommendations remain current.

4. *Recommendation (new):* Establish databases for appropriate samples and clinical information to facilitate future large-scale multicenter collaborations on genetic contributions to endometriosis.
5. *Recommendation (new):* Collect large sample sets with appropriate clinical and phenotypic information about endometriosis for future functional studies.

One objective of genetic studies is to identify the specific genes and biological pathways responsible for increasing disease risk. The gene discovery phase only identifies genomic regions associated with disease, and the next critical steps are to link the DNA sequence variation to the altered regulation and function of specific genes. Defining these molecular mechanisms for each genomic region is a major challenge.[40,41] The general approaches include "fine mapping" of the association signal in each region with additional genotyping, functional annotation, expression quantitative trait locus studies for target-gene identification using global and local gene expression studies, and evaluation of likely causal SNPs and target genes by genomic and functional studies. Studies would be strengthened if there were comprehensive data available for global regulation of gene expression and epigenetics in relevant reproductive tissues, but these data are not currently available.

There is accumulating evidence that epigenetic mechanisms (that are able to alter the effect of genes without changing the DNA "code") may play an important role in endometriosis. Most epigenetic-focused studies to date have been investigations of promoter methylation of genes known to be differentially regulated in endometriosis: either silenced (eg, *p21*, *CDH1*, *PRB*, *HOXA10*, *17HSD2*, aromatase, and *ESR1*) or upregulated (eg, *SF1*).[42-45] Together, these molecular

aberrations may sustain the survival and growth of ectopic implants and explain differences in disease aggressiveness and invasive properties.[46-48]

Genome-wide methylation signatures in isolated stromal cells obtained from eutopic endometrium and ectopic tissue from cell walls of ovarian endometriomas identified a unique epigenetic fingerprint in endometriosis, suggesting that altered DNA methylation is an integral component of the disease.[49] Results further suggest a novel role for the GATA family as key regulators of aberrant DNA methylation in endometriotic cells. Results from Illumina 450K methylation chips in DNA samples from the endometrium from 31 patients with endometriosis and 24 healthy women reported a large influence of stage of the menstrual cycle methylation patterns and a small number of significant differences between cases and controls.[50] Although further studies are required to confirm the direction of causation and role of these altered methylation signatures, large epigenetic studies offer important novel approaches. Recent analyses in other traits show environmental factors contributing to methylation differences and that genome-wide methylation signals can be combined with genome-wide genetic data to aid risk prediction.[25,51]

Although DNA methylation has received considerable attention, little is known about the role of histone modifications in endometriosis. Histone deacetylase inhibitors (HDACi) and other epigenetic modulators are emerging as a class of promising cancer therapeutics.[52,53] During the last decade, many drugs with histone deacetylase (HDAC)–inhibiting action have been shown to induce growth arrest, apoptosis, and differentiation of tumor cells.[54,55] It was recently shown that different types of lesions vary in the expression of HDACs[56,57] and that tissues (lesions and endometrium) from patients have different levels of H3K9 and H4K16 acetylation compared to control tissues.[58,59] Thus, evidence has started to accumulate that endometriotic lesions have a characteristic histone code and that global H3 and H4 acetylation within promoter regions of candidate genes is differentially modulated in lesions.

More recently, histone methylation has been identified as another potential target for therapy, following the discovery of enzymes that modulate this specific modification of histones, histone methyltransferases (HMTs), and histone demethyl transferases.[60,61] A growing number of HMT inhibitors (HMTi) are undergoing intense research efforts as potential treatments for cancer, based on the observation that these enzymes are at increased levels in various cancer types. It will be of interest to explore this new, promising avenue for targeted treatments of endometriosis. In conclusion, based on the data obtained to date, endometriosis may have an important epigenetic component involving nucleoside and histone modifications; as such, this disease is a good candidate for epigenetic reprogramming through HDACi and HMTi that should be explored further.[62,63]

6. *Recommendation (new):* Studies should be undertaken on all aspects of epigenetic regulation of endometriosis.

Functional Biology

There were a total of 25 recommendations relating to pathophysiology of endometriosis developed at the 2011 Montpellier consensus conference. The consensus of the participants was that each of these remained relevant and that none had been fully addressed. Among the earlier recommendations, some were updated in 2014 to conform more closely to evolving research concepts. Examples of this include new data emerging about the location of putative progenitor cells as well as studies in models highlighting the inherent "plasticity" of cells within the endometrium that make likely the existence of cells that may change their identity via mesenchymal/epithelial transition.

7. *Recommendation (updated):* Further research is required into all aspects of endometrial progenitor cell biology, including their origins, their potential to adopt different cell lineages, and whether inhibiting the recruitment and differentiation of progenitor cells will limit the progression of endometriosis.

8. *Recommendation (updated):* Research should be directed toward understanding the phenotype of immune cells such as macrophages and mast cells in endometriosis lesions.

9. *Recommendation (new):* There should be investigation of the epithelial-to-mesenchymal transition state, well characterized in cancer metastasis, which may prove to be informative regarding the invasiveness of endometriosis lesions.[64-67]

Despite the many unchanged recommendations from 2011, it was noted that the literature on endometriosis continues to be compromised by studies that fail to differentiate between the location and type of lesion being studied. It was suggested that reviewers should insist on this information being included before papers are accepted and suggested that WERF EPHect Surgical Form be utilized for harmonization of data reporting.

Several updated or new recommendations on the functional biology of endometriosis were tabled at the 2014 Sao Paulo workshop, covering animal models, imaging, immune and progenitor cells, peritoneum, and pain. A new mouse model using "menstrual" uterine tissue from a donor mouse has been developed: Insights from this model include the potential for immune cells such as macrophages that are shed into the peritoneal cavity at the time of menses persisting in lesions and contributing to the growth of both vascular (angiogenesis) and nerve cells (neurogenesis) within the lesions.[68] In the last 3 years, there has been a much greater appreciation that macrophages are not the only cell type that has the potential to play an important role in establishment of lesions and development of pain symptoms, as well as a major reevaluation within the macrophage research community of their phenotypic classification.[69]

10. *Recommendation (new):* Studies focusing on the role of macrophages should consider the contribution from

the endometrium[70] as well as the peritoneum and use new macrophage classification systems.[71]

11. *Recommendation (new):* Studies on mast cells should be conducted to assess their contribution to development of pain and other symptoms,[72] building on historical preliminary data.[73]

New insights have been gained from studies on peritoneum highlighting changes in women with chronic pain, even if they do not have active or visible endometriosis,[74,75] metabolic changes, and a role for transforming growth factor β.[76,77] These studies will inform future development of nonsurgical treatments. The link between pain and pathology has only been possible because of the use of standardized measures of pain intensity.[4]

12. *Recommendation (updated):* Studies on the peritoneum should be encouraged and used to complement those on endometriosis lesions. Cell models including mesothelium from the peritoneum of women having chronic pain should be used to extend investigations on intact human lesions/peritoneal tissue.

Symptoms

Pain

Very little progress has been made recently in either understanding the mechanisms underlying endometriosis-associated pain or in identifying effective treatment strategies for this symptom. It is now well established in the pain community (among both scientists and clinicians) that central changes occur in all chronic pain conditions and that the nervous system can both modulate pain or may itself be responsible for generating the sensation of pain.[78] There is good evidence that these changes also occur in conditions associated with pelvic pain[79-81] including endometriosis.[82,83] However, in the majority, these studies are descriptive, providing no information on cause and effect nor relating central changes to potential pain generators in the periphery.

A large number of factors have been found to be altered in the pelvises of women with endometriosis when compared to controls (eg, inflammatory mediators, neoangiogenesis, nerve density, transient receptor potential cation channel subfamily V member 1 expression [TRPV1]), which may plausibly be involved in generating pain.[84] However, there is little relationship between the magnitude of these alterations and the intensity of the pain experienced.

Two recent studies have demonstrated how, by combining information about the structure or function of the nervous system with clinical descriptors and peripheral measures, insights into the mechanisms generating pain can be found. First, it was shown that levels of cytokines in the peritoneal fluid of women with endometriosis (particularly tumor necrosis factor α) were related to neurophysiological measures of central hyperexcitability in response to painful stimuli.[85] Second, brain volume was investigated in 4 groups of women: (1) healthy controls, (2) women with CPP without endometriosis, (3) women with CPP and endometriosis, and (4) women with endometriosis but no associated pain.[86] Perhaps unsurprisingly, women with CPP had alterations in gray matter volume consistent with findings in other chronic pain conditions,[87] whether they had endometriosis. However, more interestingly, the women with endometriosis but no pain had an increased volume of the periaqueductal gray, a key region of the descending pain modulatory system (DPMS). As the DPMS acts to control the amount of information ascending to the brain from the dorsal horn of the spinal cord, and dysfunction within this system has been proposed as a potential mechanism leading to pain vulnerability,[88] this may be an example of adaptive brain plasticity preventing some women with endometriosis from experiencing pain. Of note, there is now an increased interest in dysmenorrhoea within the pain community[89] since the recent publication of 4 studies demonstrating long-lasting structural and functional changes within the brains of women with dysmenorrhoea.[90-93] Furthermore, dysmenorrhoea was recently reclassified as a chronic pain condition by the International Association for the Study of Pain (IASP).[94]

Endometriosis is unusual in the context of chronic pain conditions because of the number of different types of pain (eg, dysmenorrhoea, noncyclical pelvic pain, dyspareunia, etc) that can be experienced by any 1 woman, potentially all with different underlying mechanisms and associations. Moreover, the relative severity of this pain varies among patients and over time. Potentially one of the factors hampering progress in our understanding of endometriosis-associated pain is the use of crude or inadequate measures of pain that do not account for these differing types of pain or for the quality of the pain (stabbing, burning, aching, etc) or for variation with the menstrual cycle. The use of standardized questionnaires for data collection as proposed by EPHect[4] is expected to help in this respect with regard to mechanistic and biomarker studies. However, for clinical trials, the design of a novel patient report outcome measure (PROM) that is meaningful to patients is necessary. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials have previously defined core outcome measures that should be included in any trials in chronic pain,[95] and it was proposed a few years ago that these should be adapted for clinical trials in endometriosis-associated pain rather than designing completely new unvalidated measures.[96] Any such PROM should include measures of other factors contributing to the pain experience such as psychological state and pain catastrophizing as these have also been shown to contribute to perceived quality of life[97,98] and success of treatment.[99,100]

Two new animal models have been used to investigate the link between estrogen and pain. Evidence that estrogenic ligands may directly regulate factors such as Slits[101] and production of inflammatory factors by macrophages[102] known to regulate nerve cell migration has been obtained using the new mouse model, demonstrating its potential as a platform for basic research and testing of potential therapies to treat

endometriosis-associated pain using Von Frey and other techniques. A rat model has been developed in which endometrial tissue is transplanted to the gastrocnemius muscle; this has subsequently been used to explore the role of leptin in estrogen-dependent chronic pain.[103-105]

Five recommendations on endometriosis-related pain were unchanged from 2011, whereas 2 were either no longer relevant or superseded.

13. *Recommendation (updated):* All studies collecting any form of biological measure (eg, inflammatory marker, gene expression, nerve density, etc) need to also collect detailed pain information rather than a single rating of "generalized pelvic pain intensity" to allow a better understanding of pain mechanisms in endometriosis.
14. *Recommendation (updated):* An endometriosis or female pelvic pain–specific PROM should be developed to capture the various different types of pain (dysmenorrhoea, dyspareunia, noncyclical pelvic pain, dyschezia, dysuria, etc), their quality (eg, burning, aching, stabbing), and any cyclicity.
15. *Recommendation (new):* Where possible, endometriosis-associated pain should be phenotyped by its underlying mechanisms (eg, inflammatory, neuropathic, central, etc).[106]
16. *Recommendation (new):* Encourage the use of new rodent models to test existing drugs that may be suitable for repurposing as treatments for inflammation/pain in women with endometriosis.
17. *Recommendation (new):* Engage the leaders of large multinational studies launched recently to evaluate adolescent brain development with biobanking of brain imaging data and to ensure that pain and dysmenorrhea data as well as endometriosis diagnoses are included in their data collection efforts.

In common with other chronic pain conditions, potential novel treatments for endometriosis-associated pain have rarely been successful in early-phase clinical trials. One potential explanation for this observation is that the mechanisms generating pain are so variable in this heterogenous population that there will not be a "one-size-fits-all" treatment. The strategy of sensory phenotyping, which has been proposed particularly in neuropathic pain but also applied to other chronic pain conditions, is particularly interesting in this context. This strategy uses the pattern of sensory symptoms and pain qualities derived from the completion of questionnaires and the results of quantitative sensory testing to classify patients on the basis of the potential site(s) of dysfunction of the pain processing pathways. Detailed analysis of large numbers of patients with neuropathic pain with a variety of etiologies has shown that it is feasible to subgroup patients with this strategy, and moreover, retrospective analysis of clinical trial data has shown the sensory phenotype to predict the response to treatment.[107] Thus, any PROM designed for women with CPP/endometriosis should contain sufficient information to allow such stratification to be performed and to facilitate multicenter proof-of-concept studies to confirm that such a strategy is appropriate in endometriosis. It is promising, however, that in other conditions not classically considered as neuropathic, preoperative central measures have been shown to both predict the response to surgery and the development of chronic postoperative pain.[108-110]

Although it is disappointing that endometriosis rarely features on the programs of specialist pain meetings, there is a similarly poor inclusion of pain neuroscience in the majority of Endometriosis or Women's Health conferences. Given that CPP, with or without endometriosis, affects millions of women worldwide, inclusion of pain neuroscience more broadly in health and research meetings is essential. Furthermore, many of the topics discussed at the WCE in Sao Paolo (eg, the role of gases such as nitric oxide and hydrogen peroxide in generating pain, neurogenic inflammation, pain genetics, and patient tailored treatment) were also discussed in headache and pain meetings that same year (15th World Congress on Pain, October 6–11, 2014, Buenos Aires, Argentina. 2nd Joint Symposium of IASP/International Headache Society [IHS], April 23–26, 2014, Siena, Italy). Thus, it is proposed that the collaboration and sharing of knowledge and experience with pain neuroscientists will be key to unraveling the peripheral and central mechanisms generating the clinical experience of pain in women with endometriosis.

18. *Recommendation (new):* A joint research symposium between pain researchers and endometriosis researchers should be organized to share knowledge, identify areas of overlap, optimize potential collaborations, and avoid "reinventing the wheel."
19. *Recommendation (new):* Research should be undertaken to analyze community attitudes to CPP using sociological methods.

Infertility

It is estimated that up to 35% to 50% of women with infertility have endometriosis.[111] Whether endometriosis contributes to infertility has long been debated, and underlying mechanisms resulting from the presence of disease and classified by stage possibly affecting fertility potential are poorly understood, although inflammation and reactive oxygen species are believed to contribute significantly.[5,112] To date, data support abnormal folliculogenesis, including compromised granulosa cell and follicle immune homeostasis, lower oocyte quality and reduced ovarian reserve, lower fertilization rates, altered embryo development, and abnormalities in the eutopic endometrium that affect implantation success in a disease stage–specific manner.[112-115] There are also consequences of anatomical distortion that may compromise fertility,[112] and

there are mixed data on pregnancy outcomes in women with disease.[116,117] Human in vitro fertilization (IVF) and embryo transfer and ovum donor/recipient cycles serve to test hypotheses generated from experimental data obtained in animal models and with human endometrial and endometriosis tissues and cells.[118,119] Overall, studies of various factors contributing to endometriosis-related infertility show conflicting results.[120] This lack of identified factors underscores the need to have rigorous epidemiological and clinical data to understand mechanisms underlying effects of endometriosis on female fertility, assess approaches to mitigate these abnormalities for treatment and also for diagnosis and prevention, and understand short-term and long-term effects of endometriosis-related infertility and treatment on the health of affected women and their offspring.

There were no previous recommendations on infertility associated with endometriosis, and 3 new recommendations were proposed.

20. *Recommendation (new):* Research is needed to elucidate the causal relation, if one exists, between endometriosis and infertility, taking into account the importance of evaluating the relationship between pelvic pain and infertility, independent of endometriosis.

21. *Recommendation (new):* Determine the relative contribution of anatomic versus nonanatomic endometriosis-associated lesions, including the role of adhesions, to infertility in general and embryo implantation rates in particular.

22. *Recommendations (new):* Develop validated screening tools including clinical history and physical examination to reduce the number of patients treated by laparoscopy, so that when laparoscopy is used for endometriosis-related infertility, it is used effectively.

Oocyte Competence, Folliculogenesis, Embryo Quality, and Development

Several studies strongly support the view that oocytes from women with endometriosis have reduced competence. The proinflammatory environment in which the oocyte matures likely affects its developmental potential, and several animal studies support this view.[121] Clinical IVF studies that have assessed fertilization rates, embryo quality, and implantation rates with oocytes from women with endometriosis have either not found significant differences[122,123] or have found significantly decreased oocyte competence.[118] Reduced oocyte competence results in early embryonic growth arrest[124] and reduced embryo quality and implantation rates.[125] A retrospective meta-analysis of IVF outcomes in patients with endometriosis has highlighted a progressive decrease in oocyte quality with increasing stage of disease[126] and more compromised oocyte quality in women with endometriomas.[123] Also, the latter subtype has lower ovarian reserve that can translate to lower oocyte quality/competence.

23. *Recommendation (new):* Investigate the effects of endometriosis on folliculogenesis, oocyte competence, and subsequent fertilization and embryo quality. Studies should include detailed information on endometriosis stage and involvement of the ovaries with disease.

24. *Recommendation (new):* Investigate the mechanisms underlying diminished ovarian reserve in women with endometriosis, the degree to which this is spontaneous due to ovarian endometriosis or endometriomas, or due to surgical intervention, and determine how much of the observed diminished ovarian reserve is reversible.

Endometrial Abnormalities and Pregnancy Outcomes

There are abundant data to suggest that the endometrium of women with endometriosis demonstrates abnormalities in gene expression, global transcriptome, signaling pathways, in response to steroid hormones, and having a proinflammatory environment.[127-129] Only a few studies have looked at the influence of disease stage[129] or considered other uterine and pelvic abnormalities as confounders.[130] To date, women with more advanced compared to early-stage disease have more difficulty getting pregnant,[131] significantly lower implantation rates (13.7% vs 28.3%, respectively; $P < .05$) and pregnancy rates (22.6% vs 40.0%, respectively; $P < .01$), but not fertilization or miscarriage rates,[132] and significantly lower IVF pregnancy rates (13.84% vs 21.12%, respectively; $P < .001$),[126] underscoring a potential endometrial origin of these differences. Also, patients with advanced disease demonstrate diminished ovarian response and higher cancellation rates in IVF cycles but after surgery show improved implantation, pregnancy, miscarriage, and delivery rates, similar to those of women with tubal factor infertility,[122] suggesting that removal of disease improves endometrial receptivity to embryonic implantation.

There is increasing evidence that endometriosis during pregnancy can present diagnostic and therapeutic challenges and can predispose to complications that can affect the mother and the outcome of the pregnancy.[133] For example, ovarian endometriomas with pregnancy-associated decidualization can have characteristics of malignancy, and extensive adhesions and/or disease growth can lead to bowel perforation, appendicitis, spontaneous hemoperitoneum, endometrioma infection or rupture, and other complications.[133] Abnormal subendometrial myometrial peristalsis and the inflammatory component of endometriosis have been proposed to predispose to abnormalities in placentation (eg, placenta previa), placenta vasculogenesis and hypertensive disorders in pregnancy, preterm birth, fetal growth restriction, and miscarriage.[133,134] Exact mechanisms underlying these risks in the setting of a history of endometriosis in pregnant women warrant further investigation.

25. *Recommendation (updated):* There is a need for reliable and comprehensive epidemiological data on pregnancy outcomes in women who have endometriosis who become pregnant naturally by infertility therapy and assisted reproduction.

26. *Recommendations (new):* Data on clinical outcome after infertility treatment, whichever type, medical, surgical, expectant, should be collected with time to pregnancy as a key important event, using life table analysis and cumulative pregnancy rates at the expected level of quality in any fertility trial.
27. *Recommendations (new):* Capture a history of endometriosis (stage, treatment to become pregnant if relevant) in obstetrical records, working with professional organizations to promote the inclusion of endometriosis as a diagnosis in the obstetrical record.

Pain and Optimal Fertility Therapies for Women With Endometriosis, Disease Status

An unmet need was identified to assess pain during fertility treatment and management of pain, including safety, efficacy, and effects on quality of life.

28. *Recommendations (new):* There is a need to determine whether women with endometriosis experience pain during infertility therapy, and if they do, whether it is exacerbated by fertility treatment, and if/how the pain affects both quality of life and fertility. There is also a need to determine whether treatments for pain during fertility therapy are safe and efficacious, and whether they alter the efficacy of fertility treatments.

Patient Perspectives

Although previous research priorities workshops in 2008 and 2011 included consumer representatives, there were no recommendations specifically formulated toward research either into or driven by patient perspectives. The 2014 workshop sought to remedy this and agreed that future workshops should continue to include a session on the perspectives of women with endometriosis. A number of new recommendations were developed.

29. *Recommendation (updated):* Patient views on the most pressing topics in endometriosis research and clinical priorities should be sought and subcategorized into different demographic groups including age, symptoms, ethnicity, and economic background.
30. *Recommendation (new):* Research should be undertaken on how treatment costs, including for IVF, impact on the patients' decisions around diagnosis and treatment.
31. *Recommendation (new):* In both developed and emerging countries, adolescent beliefs about not having periods and about the use of contraceptives when they are not sexually active should be explored. The need for improved education programs and/or patient support organizations should be quantified, particularly in emerging countries.

Diagnosis, Classification, and Prognosis

Surgery

Diagnostic surgery for endometriosis. The clinical utility of the revised American Society for Reproductive Medicine (rASRM) classification system[135] for endometriosis-related infertility, pain, and deep infiltrating endometriosis is limited. A surgical classification system for endometriosis-associated infertility[136] has been developed and its clinical prognostic usefulness validated in 10 independent trials. Classification systems for deep infiltrating endometriosis are also being developed (AAGL and ENZIAN).

The meeting recognized the need for improved education and training to increase uptake of minimally invasive diagnostic imaging technologies. Preoperative imaging will reduce the likelihood of laparoscopic procedures, which have to be abandoned because of unexpectedly severe disease. In the future, symptomatic women who have been diagnosed preoperatively with moderate to severe disease by imaging modalities should be offered excisional surgery as a first-line treatment. If imaging studies reveal no obvious signs of endometriosis, then "see-and-treat" surgery should be considered for women with pain or infertility who are refractory to nonsurgical therapies.

Diagnostic imaging modalities allow for better preoperative planning and counseling for patients scheduled to undergo excisional surgery for deep endometriosis, reducing both the morbidity and treatment cost of endometriosis.[137] Reduced reliance on diagnostic and "staging" surgery and improved education about and access to endometriosis-specific ultrasonographic and magnetic resonance imaging (MRI) techniques is desirable.[138] However, diagnostic surgery is still relevant for superficial and/or mild peritoneal disease, which remains difficult to detect using imaging modalities alone in symptomatic women.[139]

Controversy also remains in young women, who are thought to have mild disease, as to the need for a surgically defined diagnosis when treating pain symptoms.[140] It was acknowledged that imaging techniques, such as transvaginal ultrasound (TVUS), may be inappropriate and less able to detect disease in this group.[141] For this reason, it is still recommended that adolescents who have failed hormonal and pain therapies be offered surgery to establish a diagnosis, as more than two-thirds will likely have disease,[142,143] with some evidence that the frequency of minimal–mild endometriosis is actually lower in adolescents than adults.[144]

32. *Recommendation (new):* The development, validation, and implementation of new endometriosis classification systems should continue.
33. *Recommendation (new):* For patients at low risk of deep endometriosis, efforts should be made to improve and evaluate the development of low-cost advanced diagnostic surgical techniques (eg, single-port entry and natural orifice translumenal endoscopic surgery [NOTES] methods) in centers with advanced training and accreditation standards.

Imaging

Different imaging modalities play an essential role in the diagnosis and perioperative management of endometriosis. While operator experience as well as lack of sensitivity to detect minimal and mild endometriosis can be problematic, ovarian endometriosis (endometrioma) and deep endometriosis can be readily recognized using TVUS and/or MRI.[145,146] Diagnostic test accuracy (DTA) studies and meta-analyses have been performed and show that TVUS and MRI techniques can diagnose endometriomas, rectosigmoid, and deep infiltrating endometriosis with a similar sensitivity and specificity to that of surgery.[147]

At the 2011 meeting, it was recognized that technological advances in imaging were evolving rapidly and that consequently imaging techniques should be monitored on an ongoing basis for application to endometriosis. This recommendation was updated in 2014.

There have been significant advances in MRI and imaging related to pain since the 2011 meeting. Recent work in an animal model to detect endometriosis noninvasively using dynamic contrast-enhanced MRI with gadofosveset–trisodium as a contrast agent[148] found that contrast-enhanced MRI gave better visualization than conventional MRI. The MRI, including diffusion tensor imaging with tractography, is a noninvasive means of detecting changes in the microarchitecture of the sacral nerve roots. The MRI is increasingly used for endometriosis and CPP, and tractography can be used to show altered microstructure of sacral roots affected by endometriosis and CPP.[149]

It is now possible under certain circumstances to image nerves and alterations in nerve properties noninvasively, to image receptor level expression and inflammatory processes in injured tissue, to image astrocyte and glial roles in neuroinflammatory processes, and to image pain conduction functionally in the trigeminal ganglion.[150] These advances will ultimately allow description of the pain pathway from injury site to behavioral consequence in a quantitative manner. Such a development could lead to diagnostics determining the source of pain (peripheral or central), objective monitoring of treatment progression, and, hopefully, objective biomarkers of pain.[150]

34. *Recommendation (updated):* More research is needed with emerging imaging modalities to define whether they are suitable for identifying lesions and peripheral pain pathways.
35. *Recommendation (new):* More longitudinal studies are needed based just on imaging techniques to track the course of the disease and determine which patients ultimately require surgery.
36. *Recommendation (new):* Investigate clinical outcomes in patients randomized to surgical versus nonsurgical treatment based on diagnostic imaging.
37. *Recommendation (new):* Develop a validated screening tool based on history and physical examination to identify women who should undergo imaging, particularly for adolescents and early-stage lesions.
38. *Recommendation (new):* Prospective studies should be undertaken that can define changes in clinical practice and any resulting cost savings when diagnostic imaging tests are introduced into clinical algorithms.
39. *Recommendation (new):* More high-quality DTA studies based on Quality Assessment of Diagnostic Accuracy Studies (QUADAS) are needed to ensure accurate assessment of the best diagnostic imaging modalities.

Biomarkers

Of the 2 recommendations from 2011 concerning biomarkers, both were considered still relevant and not in need of updating. In addition, a number of new recommendations were put forward. There was emphasis placed on the need for the discovery of new biomarkers to assist with diagnosis and classification of endometriosis.

Laparoscopic identification coupled with histological verification is currently the gold standard for diagnosis of endometriotic lesions.[139] Benefits of this approach include the simultaneous treatment of the condition and reassurance for both patient and clinician. However, medical treatments can also be similarly successful but may be associated with side effects, whereas surgery despite being effective in many cases is still associated with the risk of morbidity and mortality. Hence, the availability of robust biomarkers to aid clinical decision-making continues to be a major unmet need.

Two systematic reviews using well-defined QUADAS criteria summarized the results from the existing biomarker studies.[127,151] The authors included 343 studies conducted since January 1984 on biomarkers in peripheral blood, saliva, urine, and eutopic endometrium. Despite an abundance of potential candidates, no biomarker was found to be suitable for clinical application.[139] Almost all studies were underpowered, had significant methodological issues, or demonstrated a poor choice of control patients. In addition, in some cases, different studies investigating the same marker demonstrated opposing findings, largely a result of factors such as the heterogeneity of the disease, patients and controls, different collection and processing techniques of biological samples, and nonstandardized assessment of clinical data. Many of these standardization issues have been addressed by the recent EPHect publications.[3,4,11,12]

One important study tested a panel of 28 biomarkers identified from the literature in 232 women with endometriosis and 121 control women.[152] A strength of this work is that the findings from a training set were then validated with the test set. A lack of validation studies was one of the main points of criticism of all the other existing studies.

40. *Recommendation (new):* Large databases from collaborative efforts using harmonized and robust sample

and data collection tools are needed to help identify and validate the biophenome of endometriosis.

41. *Recommendation (new):* Multicenter studies of the biophenome should incorporate well-selected control populations including women with other pelvic diseases to achieve a high sensitivity and specificity and should focus on both discovery and validation phases.

42. *Recommendation (updated):* Efforts should be made to combine noninvasive biomarkers, imaging, and clinical characteristics to improve DTA.

It is important to emphasize the lack of data on endometriosis in adolescent girls. It has been recognized that the condition and associated symptoms are present in this age group, but that the few existing studies involve small numbers of patients, which make it impossible at present to draw any reliable clinical conclusions.[140] Therefore, a research focus on adolescent girls with symptoms suggestive of endometriosis is urgently needed. One such clinical observation that may point to early-onset endometriosis is neonatal uterine bleeding detected in 5% of neonatal girls around day 4. This withdrawal bleed resulting from maternal hormone withdrawal may be refluxed into the pelvic cavity due to the functional occlusion of the long neonatal cervix. Endometrial stem cells so delivered may remain dormant until menarche where they become activated to initiate growth of endometriosis lesions.[153] Although some 10 years will be required to collect these data prospectively, it will determine whether neonatal menstruation is a risk factor and potential biomarker for adolescent disease.[154]

43. *Recommendation (new):* In addition to adolescents and women with pain symptoms, emphasis should be placed on biomarker studies in adolescents and women with subfertility.

44. *Recommendation (new):* Systematic registration of neonatal menstruation should be encouraged in maternity services as a potential biomarker of early-onset endometriosis.

Accumulating evidence demonstrates that genetic factors play a role in endometriosis (see above). Genome-wide association studies have identified SNPs linked to increased risk of endometriosis at a number of genetic loci in women, especially in those with extensive disease.[30,31,34,155,156] Recent advances in laboratory techniques and network analysis now allow for large-scale functional, multiplex studies combining results from different approaches, which may not only advance our understanding of disease pathogenesis mechanisms but also identify novel target candidates for diagnosis and treatment.

45. *Recommendation (new):* Results from large-scale genetic studies should be followed up by functional multiplex biomarker studies.

Disease and Symptom Management

Surgery

There has been significant progress made on surgery-related recommendations formulated at the 2008 Research Directions Workshop,[1] as summarized in the following 2 paragraphs.

Combined surgery and ovarian suppression results in better outcomes in patients with pain.[157] Laparoscopic surgery to treat mild and moderate endometriosis reduces overall pain and increases live birth or ongoing pregnancy rates. There is low-quality evidence that laparoscopic excision and ablation were similarly effective in relieving pain, although there was only one relevant study.[158] Reasonable data have demonstrated that laparoscopic treatment has adverse outcomes no worse than other surgical interventions. Shaving, disc resection, and bowel resection all have a role in management of bowel endometriosis, but further elucidation of their application is needed.[159]

The EFI[136] has been validated as a useful clinical tool in 10 additional published studies. Excisional surgery improves spontaneous pregnancy rates in the 9 to 15 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone.[157] Ovarian reserve may be reduced with the treatment of endometriomas, but its clinical significance is variable.[160,161]

There were 5 major recommendations relating to surgery from the 2011 workshop,[2] and all of these still remain relevant. In addition, 2 new recommendations have been made in 2014. Perhaps the most important of these arise from the recognition that no classification system predicts pelvic pain outcomes following surgery.[157]

46. *Recommendation (new):* Principles utilized in development of the EFI[136] should be utilized in development of a classification system for management of pelvic pain.

47. *Recommendation (new):* The optimal application of surgery and specific surgical techniques, including energy techniques, need to be elucidated for endometrioma, bowel, bladder, ureter, and deep infiltrating endometriosis. Short- and long-term outcomes, including efficacy related to symptoms of infertility and pain, cost, and safety, need to be evaluated against nonsurgical techniques such as ovarian suppression, mind/body approaches, assisted reproductive technology (ART), and other medical and holistic interventions. This will provide information to develop improved comprehensive management approaches over time.

Medication

Disappointingly, there has been little research progress in medical management for endometriosis over the last 3 years due to the typically poor quality of the trials in this field. In March

2014, Brown and Farquhar published a summary of the evidence from Cochrane systematic reviews on treatment options for women with pain (or subfertility) associated with endometriosis.[157] They noted that the quality of the trials for specific comparisons ranged from "very low" to "moderate." The main reason identified for the poor trial quality was bias: inadequate reporting of allocation concealment and randomization methods and a lack of blinding.

48. *Recommendation (updated):* 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 ideally against placebo and against defined outcome measures.

Although there were 31 "open" (recruiting or about to start) relevant trials at the time of the Sao Paulo meeting addressing treatment efficacy of endometriosis registered on ClinicalTrials.gov and the EU Clinical Trials Register, only 1 trial (PRE-EMPT http://www.controlled-trials.com/ISRCTN97865475) directly addresses a 2011 recommendation. This trial aims to determine whether effective medical adjuvant therapies exist to prevent or limit the recurrence of lesions and symptoms following surgery.

As a consequence of the overall lack of progress in clinical trials, most recommendations from 2011 remain substantially unchanged, although a number have been updated.

The precise mechanisms by which endometriosis causes pain are not completely understood (see above). However, there is increasing evidence that pain may be due to neuropathic, in addition to nociceptive and inflammatory, mechanisms.[162] The efficacy of neuromodulatory drugs has been documented for a number of neuropathic pain conditions,[163,164] but not for endometriosis-associated pain specifically. In some of these trials, neuromodulators also improved sleep, mood, and other elements of quality of life.

49. *Recommendation (updated):* Clinical trials are needed to evaluate treatment options for pelvic pain associated with endometriosis, including neuromodulatory drugs used in the treatment of other chronic pain conditions.

Current treatment strategies for endometriosis are restricted to surgical excision of the lesions or suppression of ovarian function and estrogen action. In up to 75% of cases, symptoms recur after surgery, and long-term ovarian suppression is often ineffective, suppresses fertility, and has unwelcome side effects.[165] What women with endometriosis want is a therapy that can (1) reduce the painful symptoms associated with the condition, (2) preserve their ability to get pregnant while on medication and (3) have no, or limited, side effects. There is, therefore, an unmet clinical need for new nonhormonal treatments for endometriosis.

50. *Recommendation (updated):* Novel nonhormonal medical treatments for endometriosis should be investigated.

The incorporation of genomic profiling into routine clinical practice has already been adopted for some tumors, such as human epidermal growth factor receptor 2 testing in breast cancer, providing a guide to treatment selection that is not afforded by histological diagnosis alone.[166] There is also increasing consensus that clinical trials should be more stratified for, or be performed only, in similarly "molecularly defined" subsets to avoid overtreatment and to save valuable resources.[167] This approach results in smaller numbers of more phenotypically and genotypically well-defined patients being eligible for such trials.

51. *Recommendation (new):* We need to transform our clinical study design to integrate genomic profiling for patient stratification.

Other Therapies

There were no formal recommendations concerning complementary and alternative medicine (CAM) from the 2011 workshop, although it was noted that Chinese herbal medicine (CHM) was widely used in China to treat symptoms of endometriosis such as pain and infertility and that more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.[168,169] The CAM therapies used by patients with endometriosis include herbs, acupuncture, CHM enema, microwave physiotherapy, and psychological intervention.[170] The same authors state that although CAM therapies have been gradually accepted in some countries, a range of issues hinders more widespread application of CAM therapies throughout the world. These include (1) selective publication of only positive results with varying study qualities and standards, (2) lack of large sample sizes and randomized controlled trials, and (3) the lack of confirmatory animal studies with therapies such as auricular acupoint, Chinese herbal enema, microwave physiotherapy, and psychological intervention.[170] Apart from CHM, natural products, including genistein, green tea, and resveratrol have shown effectiveness in animal studies[171-173]; however, to date, no clinical trials with these agents to treat endometriosis in humans have been reported.

52. *Recommendation (new):* There should be more research, including preclinical animal studies and randomized controlled trials, into the effectiveness of CAMs, compared to conventional therapies, for the treatment of endometriosis. These studies should include decreasing pain as well as enhancing fertility, pregnancy outcomes, and safety.

Diet and nutrition continue to be issues that women seek advice on when confronted with endometriosis. Clinical experience from practitioners present at the workshop noted that if women do modify their diet, it is often by trial and error to work out what their own triggers are. Some will find a beneficial

effect on their pain levels, but consensus on what works is not common. A similar lack of clear findings about diet and endometriosis risk is also found in the published literature, where evidence supporting a significant association between diet and endometriosis is at best equivocal.[174] Women with endometriosis seem to consume fewer vegetables and omega-3 polyunsaturated fatty acids and more red meat, coffee, and trans fats, but these findings could not be consistently replicated.[174] Others have concluded that specific types of dietary fats are associated with endometriosis and/or dysmenorrhoea, thereby indicating that there may be modifiable risk factors.[175] However, findings were equivocal and further research was recommended. There has also been a meta-analysis that found no evidence for an association between coffee/caffeine consumption and the risk of endometriosis.[176]

53. *Recommendation (updated):* Randomized controlled trials are needed to elucidate the role of diet in modifying recorded symptoms and underlying disease of endometriosis.

Patient Stratification

A number of recommendations from 2011 had some relationship to patient stratification, nearly all of which remain unchanged in this context. Patient stratification or personalized medicine is a novel concept in endometriosis. A PubMed search on May 4, 2014, using the keywords "endometriosis AND patient stratification," identified only 13 papers, with just one linking patient stratification to outcome.[177] These authors reported on a clinically relevant inflammatory network that may serve as an objective measure for guiding treatment decisions for endometriosis management and in the future may provide a mechanistic end point for assessing efficacy of new agents aimed at curtailing inflammatory mechanisms that drive disease progression.

Patient stratification is an active area of research in gynecological cancer and chronic inflammatory conditions that are common in women, especially in breast and ovarian cancer but also in rheumatoid arthritis and Crohn disease. It is important to try to apply insights from patient stratification in these related diseases to patient stratification for endometriosis. A systematic review approach is warranted to stratify predefined outcomes in endometriosis research with family history, symptoms, clinical examination, dynamic imaging/pain reporting, surgical staging, and systemic or tissue biomarkers.

Standardized baseline characteristics should be reported in clinical trials evaluating reproductive outcome in women with endometriosis, specifying completed child wish (proven fertility), absent child wish, or present child wish (active child wish at present, active child wish in the future, infertile [inability to become pregnant during the last 12 months]).[178-180]

54. *Recommendation (new):* To stratify reproductive outcome in women with endometriosis-associated infertility according to their current reproductive status and plans.

The phenotype of each patient needs to be determined and harmonized on the level of clinical symptoms, signs during clinical examination, imaging, and surgical staging. The WERF EPHect tools allow for standardized (consistent) collection of clinical symptoms and surgical findings in the context of biomarker studies,[3,4] but harmonization is also needed with respect to definitions and reporting of data related to clinical examination and imaging, in order to relate these data (ie, ovarian mass, adhesions, deep nodules, other pathology, presence/absence of pain in specific areas during examination, coexisting morbidities such as adenomyosis and fibroids) to surgical data.

55. *Recommendation (new):* To stratify clinical outcome data in medical or surgical therapeutic trials for endometriosis-associated pain and/or infertility according to predefined clinical symptoms, signs, imaging, and surgical staging.

The concept of recurrence is used differently by different authors in different studies, due to the lack of a universally accepted definition, which can be used in clinical research.[180,181]

56. *Recommendation (new):* To seek agreement on the definition of recurrence of endometriosis and endometriosis-associated symptoms after medical or surgical treatment.

Low-Income Countries and Low-Resource Settings

Previous endometriosis research priorities workshops have not considered research in low-income countries and low-resource settings.

57. *Recommendation (new):* The Workshop on Research Priorities in Endometriosis should include statements addressing the needs of low-resource settings.

Over 2 billion people live in severe poverty (World Bank data: 2.2 billion people lived on less than US$2 a day in 2011). The different approaches required in low-resource settings dictate that researchers appropriately consider the needs of the tens of millions of women in these situations. Challenges regarding culturally sensitive distribution of information, effective implementation of programs, the role of centers of excellence, private versus public initiatives/collaborations, and organizational collaborations play a critical role in developing successful interventions and research programs in low-resource settings. With the trend of delayed child bearing in emerging countries following similar patterns as has occurred in developed countries,[182] it is expected that endometriosis prevalence will rise. However, in many emerging countries, there is a lack of awareness of endometriosis among doctors, patients, and families, and there is a huge lag between emerging and

developed countries regarding endometriosis research and centers of excellence for endoscopic surgery.

58. *Recommendation (new):* Research programs run by emerging nations, targeting endometriosis-related issues specific to those nations, should be implemented.

59. *Recommendation (new):* Researchers working in developed nations should ensure that progress resulting from endometriosis research will, where possible, be of benefit in low-resource settings.

60. *Recommendation (new):* Programs and projects that provide international support and enhance regional collaboration in low-resource settings should be implemented, involving both health-care professionals and patient organizations.

61. *Recommendation (new):* We should encourage centers of excellence in developed countries to take more active role in training and supporting research programs in centers dealing with endometriosis in emerging countries and this should be part of their accreditation process.

There are almost no data on diagnosis and classification of endometriosis in low-resource settings. There has been no organized approach to obtaining such data. An endometriosis management program involving history, physical examination, testing, and management that is culturally appropriate and cost-effective and that can be used in low-resource settings needs to be developed and taken to the World Health Organization to engage them and through them health departments in the governments of the world to bring endometriosis diagnosis and treatment into their primary and secondary health-care systems.

62. *Recommendation (new):* Innovative approaches and tools such as WERF EPHect, The FIGO Fertility Toolbox, the International Committee Monitoring ART registry, and low-cost IVF should be evaluated for their possible contributions to endometriosis research in low-resource settings.

In very low-resource settings, effective family and social support may be the most important intervention to reduce the burden of disease and is applicable in any setting.

63. *Recommendation (new):* Research into culturally appropriate and cost-effective social support systems that mitigate the personal impact of endometriosis in low-resource settings should be performed.

Research Policy

Prioritization and Collaboration

At the 2011 Research Directions Workshop in Montpellier, 14 different recommendations were made under the overall banner of research policy. Of these, significant progress has been made on several, with the most obvious being the WERF EPHect. This initiative has been described in "Introduction" section.

Other recommendations from 2011, such as submission of genetic and genomic data into online repositories so as to be available for all researchers, are covered by the requirement from most international peer-reviewed journals that this is a prerequisite prior to publication. Some recommendations remain unchanged and were reinforced in 2014, the most notable being the need for a multidisciplinary and, where appropriate, multicenter approach to all aspects of endometriosis research.

There were 2 new recommendations under the heading of research prioritization.

64. *Recommendation (new):* As a priority, we should undertake multidisciplinary research aimed at producing translatable patient-based outcomes, with a particular focus on pain and infertility.

65. *Recommendation (new):* WERF should consider forming a clinical trials advisory group to provide feedback to assist researchers in developing high-quality studies that are appropriately designed and powered to achieve meaningful outcomes.

Funding Strategies

There were 3 recommendations from 2011 concerning lobbying and funding. All of these were deemed as relevant in 2014 as they were in 2011. With the global funding for research becoming more and more competitive, it has become increasingly challenging to secure funds for research in endometriosis, which despite its huge personal and health-care cost is classified as a "benign" disease. Endometriosis, however, is not benign for those who may have for decades with harsh and enduring impacts on their lives,[8] and neither is it benign when taking into consideration the personal and societal costs.[7]

Funding sources can be divided into 3 broad categories: government, philanthropic, and industry. To successfully secure funding from any of these sources, it is necessary to position endometriosis as a disease priority and commence strategic lobbying to ensure its place in national health-care and research budgets. Specific funding requests (eg, for research initiatives) may aid this process by raising awareness about the disease. To obtain philanthropic funding, endometriosis must have its profile raised through well-directed awareness campaigns, as well as targeted proposals to wealthy individuals who have the means to support women's health initiatives and who have a vested interest in supporting the eradication of a disease that may have impacted family and friends.

To ensure ongoing industry collaboration and financial support for investment in research into endometriosis disease mechanisms and improved treatments, convincing arguments must be collectively put forward to pharma to assist them in the

process of internal prioritization of specific disease investment. A disease affecting an estimated 176 million women worldwide,[183] which is not caused by preventive lifestyle factors, should provide tremendous potential for wider industry investment.

It is crucial that there is one, clear message from a large collective group of global collaborators of what needs to be done, how it will be done, and where money needs to be invested to make the goal of targeted treatments and prevention of endometriosis a reality.

66. *Recommendation (new):* Develop lobbying and fundraising resources suitable to take to government, industry, and philanthropy that highlight the social and economic cost of endometriosis, as well as the need for research to improve outcomes for women with this disease.

Lobbying resources could include regularly updated fact sheets suitable for inclusion in letters to government, online resources, and videos where women and families speak about the disease and how it has affected their lives. Successful patient advocacy groups from other diseases such as breast cancer and diabetes may be able to provide guidance and examples of approaches that have been successful in the past. The meeting noted that WERF and WES may be appropriate bodies to develop and regularly update a portfolio of suitable facts and figures for groups to use in lobbying.

Discussion

The research recommendations developed by the 2014 consensus workshop provide important new insights into the evolving challenges facing endometriosis researchers, practitioners, and patients. New areas included in these recommendations include infertility, patient stratification, epigenetics, and research in emerging countries. Patient symptoms relating to pain and infertility are the 2 areas with the most new recommendations, followed by diagnosis under headings such as imaging, biomarkers, and diagnostic surgery. This shift to more translational research priorities reflects a broader focus by government funding agencies, and society in general, toward translational research. There is also a recognition of the need to involve and harness research insights in disciplines that intersect with endometriosis (eg, pain neuroscience) and the need to broaden multidisciplinary approaches to understanding and treating endometriosis.

It is interesting to follow the evolution of research priorities from the 2008 and 2011 workshops[1,2] to present. In 2008, several of the research recommendations centered around the recognition that multidisciplinary approaches were needed and that individual silos of expertise could only make limited progress. In 2011, by far, the majority of recommendations were around functional biology and disease mechanisms, although a significant advance was the recognition of the need for more research into all aspects of endometriosis-associated pain. A key theme for 2014 has been translation to better patient outcomes.

This 2014 research priorities consensus statement builds on earlier efforts to develop research directions in endometriosis. Forty-one of the 56 recommendations from 2011 remain current. Despite this, significant progress has been made by the international research community, with more than 2500 new scientific papers listed on PubMed between the 2011 and 2014 workshops. Of note and directly emanating from recommendations at the 2011 workshop are the publications from the EPHect.[3,4,11,12] Lack of progress in other research areas may reflect the complexities of problems to be addressed, as well as the relatively slow pace of research and limited funding globally.

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 and relevant research proposals and obtain increased funding support. The recommendations also provide a document to assist in the ongoing lobbying effort for increased research funding for endometriosis research from government, industry, and philanthropy. This is particularly important in procuring funding from nontraditional sources to support research in domains that intersect with endometriosis, such as pain.

Combining the 41 recommendations that are unchanged from 2011 with the 66 new ones from 2014 gives a total of 107 current endometriosis research recommendations. A task for the participants of the next endometriosis research priorities workshop to be held at the 13th WCE on May 17–20, 2017, in Vancouver, British Columbia, Canada, will be to consolidate and prioritize these 106 recommendations, as part of developing a revised and updated set of research priorities.

Authors' Note

The complete alphabetical list representing the WES/WERF Consortium for Research Priorities in Endometriosis: G. David Adamson, Hans Albertsen, Moamar Al-Jefout, Catherine Allaire, Joe Arosh, Yana Aznaurova, Monica Brauer, Christian M. Becker, Mohamed A. Bedaiwy, Carlos Calhaz-Jorge, Sarah Choi, Kristof Chwalisz, Hilary Critchley, Marlon de Freitas Fonseca, Thomas M. D'Hooghe, Gerard A. J. Dunselman, Asgerally Fazleabas, Idhaliz Flores, Axel Forman, Francisco Garcini, Caroline Gargett, Gladis Germano, Jane Girling, Linda C. Giudice, Erin Greaves, Linda G. Griffith, Allison Hey-Cunningham, Andrew W. Horne, M. Louise Hull, Lone Hummelshoj, Neil P. Johnson, Kaori Koga, Brett McKinnon, Karen Miller, Stacey A. Missmer, Grant W. Montgomery, Annemiek W. Nap, Warren B. Nothnick, Mette Nyegaard, Michelle Park, Melissa A. Parker, Antti Perheentupa, Danielle Peterse, Marta Privato, Nilufer Rahmioglu, Peter A. W. Rogers, Edgardo Rolla, Andrea Romano, Luk Rombauts, Philippa T. Saunders, Dian Shepperson Mills, Pamela Stratton, Robert N. Taylor, Wilma Verhagen-Kamerbeck, Katy Vincent, Chi Chiu Wang, Christina Williams, Marat Zhumataev, Krina T. Zondervan.

Acknowledgments

The manuscript was prepared by the first author; all other authors contributed equally and are listed in alphabetical order. Thanks are

due to Lone Hummelshoj who provided organizational support that enabled the holding of the workshop,

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GDA is the owner of Advanced Reproductive Care, Inc and Ziva, and is a consultant to Bayer Pharma and AbbVie. HA is employed by Juneau Biosciences LLC and has direct financial interest in Juneau Biosciences. CA is a consultant to AbbVie, Actavis, and Bayer Pharma. KC is an employee of AbbVie in which he holds stock and stock options. TMD has served as advisor for Bayer Pharma, Proteomika, Pharmaplex, Astellas, Roche Diagnostics, Actavis. On October 1, 12015, TMD became vice president and head of Global Medical Affairs Infertility for Merck Serono and will continue on a part-time basis his academic appointment as a professor of Reproductive Medicine at the University of Leuven (KU Leuven) in Belgium. AF is an unpaid consultant for Abbvie and a consultant for Allergen. AF is principal investigator for a clinical trial launched by Bayer AG. LCG is an unpaid consultant to AbbVie and Nora Therapeutics. LGG consults to Amgen on nonendometriosis-related matters. LH is an unpaid consultant to AbbVie. KM is an employee of Juneau Biosciences LLC. AP consults for MSD, Merck Serono, has received lecture honoraria from MSD, Orion Pharma, and Gedeon Richter, attended a congress paid for by Ferring and is a founding shareholder in Forendo Pharma Ltd. PAWR holds research grants from and acts as an advisor to Bayer Health Care. LR is an advisor to MSD, Merck Serono, and Ferring. PS is an employee of the NIH. RNT is a consultant to AbbVie. WV-K is an employee of Roche Diagnostics International. KTZ has been a consultant to Bayer Health Care.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The workshop was funded by the World Endometriosis Society (WES) and the World Endometriosis Research Foundation (WERF). CMB holds a research grant from Bayer Health Care. HC has received travel support from AbbVie, Bayer Pharma, Gedeon Richter, Preglem, and Vifor Pharma, and holds research grants from Bayer Pharma, Preglem, the MRC (UK), and EME Program (MRC/NIHR-UK). TMD has received grants from Ferring, Merck Serono, MSD, Besins, Pharmaplex, and has received travel support from Ferring, Merck Serono and MSD. AF has grants from the NIH. IF holds a research grant from the Puerto Rico Science Technology and Research Trust. JG holds a research grant from Bayer Health Care. LCG holds a research grant from the NIH and is a shareholder in Merck and Pfizer. LGG has received research funding from Amgen and Boehringer Ingelheim. AWH holds research grants from NIHR/EME, HTA, and Chief Scientist Office. MLH holds research grants from AbbVie and Origio, has received travel expenses from Merck-Serono and Ferring, and is on the Medical Advisory board of Vifor Pharma Pty. NPJ has received travel expenses from Bayer Pharma, Merck-Serono, and MSD, and holds a research grant from AbbVie. GWM holds research grants from the Australian National Health and Medical Research Council. LR is a shareholder in Monash IVF. PTS holds a program grant from the UK Medical Research Council and a grant for Target from Bayer Pharma. PS has received research support by Allergan for the use of botulinum toxin a in studies of endometriosis-associated CPP. KV holds a research grant from Bayer Health Care. CCW holds research grants from the RGC General Research Fund (475012) and the ITC Innovation and Technology Fund (ITS/209/12). KTZ holds a research grant from Bayer Health Care Ltd.

References

1. Rogers PA, D'Hooghe TM, Fazleabas A, et al. Priorities for endometriosis research: recommendations from an international consensus workshop. *Reprod Sci*. 2009;16(4):335-346.
2. Rogers PA, D'Hooghe TM, Fazleabas A, et al. Defining future directions for endometriosis research: workshop report from the 2011 World Congress of Endometriosis in Montpellier, France. *Reprod Sci.* 2013;20(5):483-499.
3. Becker CM, Laufer MR, Stratton P, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research. *Fertil Steril*. 2014;102(5):1213-1222.
4. Vitonis AF, Vincent K, Rahmioglu N, et al. World Endometriosis Research Foundation Endometriosis Phenome and biobanking harmonization project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril*. 2014; 102(5):1223-1232.
5. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril*. 2012;98(3):511-519.
6. Hickey M, Ballard K, Farquhar C. Endometriosis. *BMJ*. 2014; 348:1-9.
7. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod*. 2012;27(5): 1292-1299.
8. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. 2011;96(2):366-373. e368.
9. Culley L, Law C, Hudson N, et al. The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update*. 2013;19(6):625-639.
10. Vercellini P, Barbara G, Abbiati A, Somigliana E, Vigano P, Fedele L. Repetitive surgery for recurrent symptomatic endometriosis: what to do? *Euro J Obstet Gynecol Reprod Biol*. 2009; 146(1):15-21.
11. Rahmioglu N, Fassbender A, Vitonis AF, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: III. Fluid biospecimen collection, processing, and storage in endometriosis research. *Fertil Steril*. 2014;102(5):1233-1243.
12. Fassbender A, Rahmioglu N, Vitonis AF, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: IV. Tissue collection, processing, and storage in endometriosis research. *Fertil Steril*. 2014;102(5):1244-1253.
13. Shah DK, Missmer SA. Scientific investigation of endometriosis among adolescents. *J Pediatr Adolesc Gynecol*. 2011;24(suppl 5):S18-S19.
14. Reis FM, Luisi S, Abrao MS, et al. Diagnostic value of serum activin A and follistatin levels in women with peritoneal, ovarian and deep infiltrating endometriosis. *Hum Reprod*. 2012;27(5): 1445-1450.

15. Zeng C, Xu JN, Zhou Y, Zhou YF, Zhu SN, Xue Q. Reproductive performance after surgery for endometriosis: predictive value of the revised American Fertility Society classification and the endometriosis fertility index. *Gynecol Obstet Invest*. 2014; 77(3):180-185.
16. Savaris RF, Nichols CR, Lessey BA. Endometriosis and the enigmatic question of progression. *JEPPD*. 2014;6(3):121-126.
17. Marziali M, Venza M, Lazzaro S, Lazzaro A, Micossi C, Stolfi VM. Gluten-free diet: a new strategy for management of painful endometriosis related symptoms? *Minerva Chir*. 2012;67(6): 499-504.
18. Durak Y, Kokcu A, Kefeli M, Bildircin D, Celik H, Alper T. Effect of vitamin C on the growth of experimentally induced endometriotic cysts. *J Obstet Gynaecol Res*. 2013;39(7): 1253-1258.
19. Harris HR, Chavarro JE, Malspeis S, Willett WC, Missmer SA. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. *Am J Epidemiol*. 2013;177(5):420-430.
20. Darling AM, Chavarro JE, Malspeis S, Harris HR, Missmer SA. A prospective cohort study of Vitamins B, C, E, and multivitamin intake and endometriosis. *J Endometr*. 2013;5(1):17-26.
21. Herington JL, Glore DR, Lucas JA, Osteen KG, Bruner-Tran KL. Dietary fish oil supplementation inhibits formation of endometriosis-associated adhesions in a chimeric mouse model. *Fertil Steril*. 2013;99(2):543-550.
22. Rudzitis-Auth J, Korbel C, Scheuer C, Menger MD, Laschke MW. Xanthohumol inhibits growth and vascularization of developing endometriotic lesions. *Hum Reprod*. 2012;27(6):1735-1744.
23. Savaris AL, do Amaral VF. Nutrient intake, anthropometric data and correlations with the systemic antioxidant capacity of women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2011;158(2):314-318.
24. Lafay Pillet MC, Schneider A, Borghese B, et al. Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case–control study. *Hum Reprod*. 2012;27(1):265-272.
25. Shah DK, Correia KF, Vitonis AF, Missmer SA. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. *Hum Reprod*. 2013;28(7):1783-1792.
26. Upson K, De Roos AJ, Thompson ML, et al. Organochlorine pesticides and risk of endometriosis: findings from a population-based case–control study. *Environ Health Perspect*. 2013; 121(11-12):1319-1324.
27. Wolff EF, Sun L, Hediger ML, et al. In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study. *Fertil Steril*. 2013;99(3):790-795.
28. Kvaskoff M, Bijon A, Clavel-Chapelon F, Mesrine S, Boutron-Ruault MC. Childhood and adolescent exposures and the risk of endometriosis. *Epidemiology*. 2013;24(2):261-269.
29. Montgomery GW, Nyholt DR, Zhao ZZ, et al. The search for genes contributing to endometriosis risk. *Hum Reprod Update*. 2008;14(5):447-457.
30. Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. *Hum Reprod Update*. 2014;20(5):702-716.
31. Albertsen HM, Chettier R, Farrington P, Ward K. Genome-wide association study link novel loci to endometriosis. *PLoS One*. 2013;8(3):e58257.
32. Pagliardini L, Gentilini D, Vigano P, et al. An Italian association study and meta-analysis with previous GWAS confirm WNT4, CDKN2BAS and FN1 as the first identified susceptibility loci for endometriosis. *J Med Genet*. 2013;50(1):43-46.
33. Sundqvist J, Xu H, Vodolazkaia A, et al. Replication of endometriosis-associated single-nucleotide polymorphisms from genome-wide association studies in a Caucasian population. *Hum Reprod*. 2013;28(3):835-839.
34. Nyholt DR, Low SK, Anderson CA, et al. Genome-wide association meta-analysis identifies new endometriosis risk loci. *Nat Genet*. 2012;44(12):1355-1359.
35. Hata Y, Nakaoka H, Yoshihara K, et al. A nonsynonymous variant of IL1A is associated with endometriosis in Japanese population. *J Hum Genet*. 2013;58(8):517-520.
36. Sapkota Y, Low SK, Attia J, et al. Association between endometriosis and the interleukin 1A (IL1A) locus. *Hum Reprod*. 2015;30(1):239-248.
37. Rahmioglu N, Macgregor S, Drong AW, et al. Genome-wide enrichment analysis between endometriosis and obesity-related traits reveals novel susceptibility loci. *Hum Mol Genet*. 2015; 24(4):1185-1199.
38. Lu Y, Cuellar-Partida G, Painter JN, et al. Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum Mol Genet*. 2015;24(20):5955-5964.
39. Lee SH, Harold D, Nyholt DR, et al. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. *Hum Mol Genet*. 2013;22(4):832-841.
40. Montgomery GW, Zondervan KT, Nyholt DR. The future for genetic studies in reproduction. *Mol Hum Reprod*. 2014;20(1): 1-14.
41. Edwards SL, Beesley J, French JD, Dunning AM. Beyond GWASs: illuminating the dark road from association to function. *Am J Hum Genet*. 2013;93(5):779-797.
42. Wu Y, Halverson G, Basir Z, Strawn E, Yan P, Guo SW. Aberrant methylation at HOXA10 may be responsible for its aberrant expression in the endometrium of patients with endometriosis. *Am J Obstet Gynecol*. 2005;193(2):371-380.
43. Wu Y, Strawn E, Basir Z, Halverson G, Guo SW. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in endometriosis. *Epigenetics*. 2006;1(2):106-111.
44. Wu Y, Strawn E, Basir Z, Halverson G, Guo SW. Aberrant expression of deoxyribonucleic acid methyltransferases DNMT1, DNMT3A, and DNMT3B in women with endometriosis. *Fertil Steril*. 2007;87(1):24-32.
45. Bulun SE, Cheng YH, Pavone ME, et al. 17Beta-hydroxysteroid dehydrogenase-2 deficiency and progesterone resistance in endometriosis. *Semin Reprod Med*. 2010;28(1):44-50.
46. Smuc T, Hevir N, Ribic-Pucelj M, Husen B, Thole H, Rizner TL. Disturbed estrogen and progesterone action in ovarian endometriosis. *Mol Cell Endocrinol*. 2009;301(1-2):59-64.

47. Brosens I, Brosens JJ, Benagiano G. The eutopic endometrium in endometriosis: are the changes of clinical significance? *Reprod Biomed Online*. 2012;24(5):496-502.
48. Cakmak H, Taylor HS. Molecular mechanisms of treatment resistance in endometriosis: the role of progesterone-hox gene interactions. *Semin Reprod Med*. 2010;28(1):69-74.
49. Dyson MT, Roqueiro D, Monsivais D, et al. Genome-wide DNA methylation analysis predicts an epigenetic switch for GATA factor expression in endometriosis. *PLoS Genet*. 2014;10(3): e1004158.
50. Saare M, Modhukur V, Suhorutshenko M, et al. The influence of menstrual cycle and endometriosis on endometrial methylome. *Clin Epigenetics*. 2016;8:2.
51. Shah S, Bonder MJ, Marioni RE, et al. Improving phenotypic prediction by combining genetic and epigenetic associations. *Am J Hum Genet*. 2015;97(1):75-85.
52. Mai A, Altucci L. Epi-drugs to fight cancer: from chemistry to cancer treatment, the road ahead. *Int J Biochem Cell Biol*. 2009; 41(1):199-213.
53. Chen H, Hardy TM, Tollefsbol TO. Epigenomics of ovarian cancer and its chemoprevention. *Front Genet*. 2011;2:67.
54. Hagelkruys A, Sawicka A, Rennmayr M, Seiser C. The biology of HDAC in cancer: the nuclear and epigenetic components. *Handb Exp Pharmacol*. 2011;206:13-37.
55. Crisanti MC, Wallace AF, Kapoor V, et al. The HDAC inhibitor panobinostat (LBH589) inhibits mesothelioma and lung cancer cells in vitro and in vivo with particular efficacy for small cell lung cancer. *Mol Cancer Ther*. 2009;8(8):2221-2231.
56. Colon-Diaz M, Baez-Vega P, Garcia M, et al. HDAC1 and HDAC2 are differentially expressed in endometriosis. *Reprod Sci*. 2012;19(5):483-492.
57. Samartzis EP, Noske A, Samartzis N, Fink D, Imesch P. The expression of histone deacetylase 1, but not other class I histone deacetylases, is significantly increased in endometriosis. *Reprod Sci*. 2013;20(12):1416-1422.
58. Monteiro JB, Colon-Diaz M, Garcia M, et al. Endometriosis is characterized by a distinct pattern of histone 3 and histone 4 lysine modifications. *Reprod Sci*. 2014;21(3):305-318.
59. Xiaomeng X, Ming Z, Jiezhi M, Xiaoling F. Aberrant histone acetylation and methylation levels in woman with endometriosis. *Arch Gynecol Obstet*. 2013;287(3):487-494.
60. Spannhoff A, Hauser AT, Heinke R, Sippl W, Jung M. The emerging therapeutic potential of histone methyltransferase and demethylase inhibitors. *ChemMedChem*. 2009;4(10): 1568-1582.
61. Piekarz RL, Bates SE. Epigenetic modifiers: basic understanding and clinical development. *Clin Cancer Res*. 2009;15(12): 3918-3926.
62. Kawano Y, Nasu K, Li H, et al. Application of the histone deacetylase inhibitors for the treatment of endometriosis: histone modifications as pathogenesis and novel therapeutic target. *Hum Reprod*. 2011;26(9):2486-2498.
63. Wu Y, Guo SW. Inhibition of proliferation of endometrial stromal cells by trichostatin A, RU486, CDB-2914, N-acetylcysteine, and ICI 182780. *Gynecol Obstet Invest*. 2006; 62(4):193-205.
64. Matsuzaki S, Darcha C. Epithelial to mesenchymal transition-like and mesenchymal to epithelial transition-like processes might be involved in the pathogenesis of pelvic endometriosis. *Hum Reprod*. 2012;27(3):712-721.
65. Cousins FL, Murray A, Esnal A, Gibson DA, Critchley HO, Saunders PT. Evidence from a mouse model that epithelial cell migration and mesenchymal–epithelial transition contribute to rapid restoration of uterine tissue integrity during menstruation. *PLoS One*. 2014;9(1):e86378.
66. Proestling K, Birner P, Gamperl S, et al. Enhanced epithelial to mesenchymal transition (EMT) and upregulated MYC in ectopic lesions contribute independently to endometriosis. *Reprod Biol Endocrinol*. 2015;13:75.
67. Nakamura M, Ono YJ, Kanemura M, et al. Hepatocyte growth factor secreted by ovarian cancer cells stimulates peritoneal implantation via the mesothelial–mesenchymal transition of the peritoneum. *Gynecol Oncol*. 2015;139(2): 345-354.
68. Greaves E, Cousins FL, Murray A, et al. A novel mouse model of endometriosis mimics human phenotype and reveals insights into the inflammatory contribution of shed endometrium. *Am J Pathol*. 2014;184(7):1930-1939.
69. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity*. 2014;41(1):49-61.
70. Thiruchelvam U, Dransfield I, Saunders PT, Critchley HO. The importance of the macrophage within the human endometrium. *J Leukoc Biol*. 2013;93(2):217-225.
71. Guilliams M, Ginhoux F, Jakubzick C, et al. Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. *Nat Rev Immunol*. 2014;14(8):571-578.
72. Kirchhoff D, Kaulfuss S, Fuhrmann U, Maurer M, Zollner TM. Mast cells in endometriosis: guilty or innocent bystanders? *Expert Opin Ther Targets*. 2012;16(3):237-241.
73. Matsuzaki S, Canis M, Darcha C, Fukaya T, Yajima A, Bruhat MA. Increased mast cell density in peritoneal endometriosis compared with eutopic endometrium with endometriosis. *Am J Reprod Immunol*. 1998;40(4):291-294.
74. Greaves E, Grieve K, Horne AW, Saunders PT. Elevated peritoneal expression and estrogen regulation of nociceptive ion channels in endometriosis. *J Clin Endocrinol Metab*. 2014; 99(9):E1738-E1743.
75. Lessey BA, Higdon HL III, Miller SE, Price TA. Intraoperative detection of subtle endometriosis: a novel paradigm for detection and treatment of pelvic pain associated with the loss of peritoneal integrity. *J Vis Exp*. 2012;(70).
76. Young VJ, Brown JK, Maybin J, Saunders PT, Duncan WC, Horne AW. Transforming growth factor-beta induced Warburg-like metabolic reprogramming may underpin the development of peritoneal endometriosis. *J Clin Endocrinol Metab*. 2014;99(9):3450-3459.
77. Young VJ, Brown JK, Saunders PT, Duncan WC, Horne AW. The peritoneum is both a source and target of TGF-beta in women with endometriosis. *PLoS One*. 2014;9(9):e106773.
78. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? *J Pain*. 2009; 10(11):1113-1120.

79. Kaya S, Hermans L, Willems T, Roussel N, Meeus M. Central sensitization in urogynecological chronic pelvic pain: a systematic literature review. *Pain Physician*. 2013;16(4): 291-308.
80. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update*. 2014;20(5):737-747.
81. Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. *Obstet Gynecol*. 2015; 125(3):719-728.
82. Mechsner S, Schwarz J, Thode J, Loddenkemper C, Salomon DS, Ebert AD. Growth-associated protein 43-positive sensory nerve fibers accompanied by immature vessels are located in or near peritoneal endometriotic lesions. *Fertil Steril*. 2007; 88(3):581-587.
83. Arnold J, Barcena de Arellano ML, Ruster C, et al. Imbalance between sympathetic and sensory innervation in peritoneal endometriosis. *Brain Behav Immun*. 2012;26(1): 132-141.
84. Morotti M, Vincent K, Brawn J, Zondervan KT, Becker CM. Peripheral changes in endometriosis-associated pain. *Hum Reprod Update*. 2014;20(5):717-736.
85. Neziri AY, Bersinger NA, Andersen OK, Arendt-Nielsen L, Mueller MD, Curatolo M. Correlation between altered central pain processing and concentration of peritoneal fluid inflammatory cytokines in endometriosis patients with chronic pelvic pain. *Reg Anesth Pain Med*. 2014;39(3):181-184.
86. As-Sanie S, Harris RE, Napadow V, et al. Changes in regional gray matter volume in women with chronic pelvic pain: a voxel-based morphometry study. *Pain*. 2012;153(5):1006-1014.
87. May A. Structural brain imaging: a window into chronic pain. *Neuroscientist*. 2011;17(2):209-220.
88. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. *Nat Neurosci*. 2014;17(2):192-200.
89. Berkley K. Primary dysmenorrhea: an urgent mandate. *Pain Clin Updates*. 2013;21(3).
90. Vincent K, Warnaby C, Stagg CJ, Moore J, Kennedy S, Tracey I. Dysmenorrhoea is associated with central changes in otherwise healthy women. *Pain*. 2011;152(9):1966-1975.
91. Tu C-H, Niddam DM, Chao H-T, et al. Abnormal cerebral metabolism during menstrual pain in primary dysmenorrhea. *Neuroimage*. 2009;47(1):28-35.
92. Tu C-H, Niddam DM, Chao H-T, et al. Brain morphological changes associated with cyclic menstrual pain. *Pain*. 2010; 150(3):462-468.
93. Tu CH, Niddam DM, Yeh TC, et al. Menstrual pain is associated with rapid structural alterations in the brain. *Pain*. 2013;154(9): 1718-1724.
94. Baranowski A, Abrams P, Berger RE, et al. Taxonomy of pelvic pain. *Classification of Chronic Pain*. 2nd ed. IASP; 2012. Published online by the International Association for the Study of Pain.
95. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106(3):337-345.
96. Vincent K, Kennedy S, Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. *Fertil Steril*. 2010;93(1):62-67.
97. Tripp DA, Nickel JC, Wang Y, et al. Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. *J Pain*. 2006;7(10): 697-708.
98. Tripp DA, Curtis Nickel J, Landis JR, Wang YL, Knauss JS. Predictors of quality of life and pain in chronic prostatitis/chronic pelvic pain syndrome: findings from the National Institutes of Health Chronic Prostatitis Cohort Study. *BJU Int*. 2004; 94(9):1279-1282.
99. Martin CE, Johnson E, Wechter ME, Leserman J, Zolnoun DA. Catastrophizing: a predictor of persistent pain among women with endometriosis at 1 year. *Hum Reprod*. 2011;26(11): 3078-3084.
100. Carey ET, Martin CE, Siedhoff MT, Bair ED, As-Sanie S. Biopsychosocial correlates of persistent postsurgical pain in women with endometriosis. *Int J Gynaecol Obstet*. 2014;124(2): 169-173.
101. Greaves E, Collins F, Esnal-Zufiaurre A, Giakoumelou S, Horne AW, Saunders PT. Estrogen receptor (ER) agonists differentially regulate neuroangiogenesis in peritoneal endometriosis via the repellent factor SLIT3. *Endocrinology*. 2014;155(10): 4015-4026.
102. Greaves E, Temp J, Esnal-Zufiurre A, Mechsner S, Horne AW, Saunders PT. Estradiol is a critical mediator of macrophage-nerve cross talk in peritoneal endometriosis. *Am J Pathol*. 2015;185(8):2286-2297.
103. Alvarez P, Chen X, Hendrich J, et al. Ectopic uterine tissue as a chronic pain generator. *Neuroscience*. 2012;225:269-282.
104. Alvarez P, Bogen O, Chen X, Giudice LC, Levine JD. Ectopic endometrium-derived leptin produces estrogen-dependent chronic pain in a rat model of endometriosis. *Neuroscience*. 2014;258:111-120.
105. Alvarez P, Giudice LC, Levine JD. Impact of surgical excision of lesions on pain in a rat model of endometriosis. *Eur J Pain*. 2015;19(1):103-110.
106. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. *Pain*. 2008;137(3):473-477.
107. Reimer M, Helfert SM, Baron R. Phenotyping neuropathic pain patients: implications for individual therapy and clinical trials. *Curr Opin Support Palliat Care*. 2014;8(2): 124-129.
108. Gwilym SE, Oag HC, Tracey I, Carr AJ. Evidence that central sensitisation is present in patients with shoulder impingement syndrome and influences the outcome after surgery. *J Bone Joint Surg Br*. 2011;93(4):498-502.
109. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138(1):22-28.
110. Weissman-Fogel I, Granovsky Y, Crispel Y, et al. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. *J Pain*. 2009;10(6):628-636.

111. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil Steril*. 2009;92(1):68-74.
112. Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A. Pathogenic mechanisms in endometriosis-associated infertility. *Fertil Steril*. 2008;90(2):247-257.
113. Garrido N, Navarro J, Garcia-Velasco J, Remoh J, Pellice A, Simon C. The endometrium versus embryonic quality in endometriosis-related infertility. *Hum Reprod Update*. 2002; 8(1):95-103.
114. Shah DK. Diminished ovarian reserve and endometriosis: insult upon injury. *Semin Reprod Med*. 2013;31(2):144-149.
115. Aghajanova L, Giudice LC. Molecular evidence for differences in endometrium in severe versus mild endometriosis. *Reprod Sci*. 2011;18(3):229-251.
116. Stephansson O, Kieler H, Granath F, Falconer H. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. *Hum Reprod*. 2009;24(9):2341-2347.
117. Brosens I, Brosens JJ, Fusi L, Al-Sabbagh M, Kuroda K, Benagiano G. Risks of adverse pregnancy outcome in endometriosis. *Fertil Steril*. 2012;98(1):30-35.
118. Simon C, Gutierrez A, Vidal A, et al. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. *Hum Reprod*. 1994;9(4): 725-729.
119. Pellicer A, Oliveira N, Ruiz A, Remohi J, Simon C. Exploring the mechanism(s) of endometriosis-related infertility: an analysis of embryo development and implantation in assisted reproduction. *Hum Reprod*. 1995;10(suppl 2):91-97.
120. Navarro J, Garrido N, Remohi J, Pellicer A. How does endometriosis affect infertility? *Obstet Gynecol Clin North Am*. 2003; 30(1):181-192.
121. Mansour G, Sharma RK, Agarwal A, Falcone T. Endometriosis-induced alterations in mouse metaphase II oocyte microtubules and chromosomal alignment: a possible cause of infertility. *Fertil Steril*. 2010;94(5):1894-1899.
122. Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril*. 2007;88(6): 1568-1572.
123. Suzuki T, Izumi S, Matsubayashi H, Awaji H, Yoshikata K, Makino T. Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization. *Fertil Steril*. 2005; 83(4):908-913.
124. Yanushpolsky EH, Best CL, Jackson KV, Clarke RN, Barbieri RL, Hornstein MD. Effects of endometriomas on ooccyte quality, embryo quality, and pregnancy rates in in vitro fertilization cycles: a prospective, case-controlled study. *J Assist Reprod Genet*. 1998;15(4):193-197.
125. Kumbak B, Kahraman S, Karlikaya G, Lacin S, Guney A. In vitro fertilization in normoresponder patients with endometriomas: comparison with basal simple ovarian cysts. *Gynecol Obstet Invest*. 2008;65(3):212-216.
126. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril*. 2002;77(6): 1148-1155.
127. May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations in endometriosis: a systematic review of putative biomarkers. *Hum Reprod Update*. 2011;17(5): 637-653.
128. Lessey BA, Lebovic DI, Taylor RN. Eutopic endometrium in women with endometriosis: ground zero for the study of implantation defects. *Semin Reprod Med*. 2013;31(2): 109-124.
129. Aghajanova L, Velarde MC, Giudice LC. Altered gene expression profiling in endometrium: evidence for progesterone resistance. *Semin Reprod Med*. 2010;28(1):51-58.
130. Tamaresis JS, Irwin JC, Goldfien GA, et al. Molecular classification of endometriosis and disease stage using high-dimensional genomic data. *Endocrinology*. 2014;155(12): 4986-4999.
131. D'Hooghe TM, Debrock S, Hill JA, Meuleman C. Endometriosis and subfertility: is the relationship resolved? *Semin Reprod Med*. 2003;21(2):243-254.
132. Kuivasaari P, Hippelainen M, Anttila M, Heinonen S. Effect of endometriosis on IVF/ICSI outcome: stage III/IV endometriosis worsens cumulative pregnancy and live-born rates. *Hum Reprod*. 2005;20(11):3130-3135.
133. Leone Roberti Maggiore U, Ferrero S, Mangili G, et al. A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. *Hum Reprod Update*. 2016;22(1):70-103.
134. Vannuccini S, Clifton VL, Fraser IS, et al. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. *Hum Reprod Update*. 2016;22(1):104-115.
135. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67(5): 817-821.
136. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. *Fertil Steril*. 2010; 94(5):1609-1615.
137. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(5):655-681.
138. Piessens S, Healey M, Maher P, Tsaltas J, Rombauts L. Can anyone screen for deep infiltrating endometriosis with transvaginal ultrasound? *Aust N Z J Obstet Gynaecol*. 2014;54(5): 462-468.
139. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29(3):400-412.
140. Brosens I, Gordts S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. *Hum Reprod*. 2013;28(8): 2026-2031.
141. Reese KA, Reddy S, Rock JA. Endometriosis in an adolescent population: the Emory experience. *J Pediatr Adolesc Gynecol*. 1996;9(3):125-128.

142. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol*. 1997;10(4):199-202.
143. Janssen EB, Rijkers AC, Hoppenbrouwers K, Meuleman C, D'Hooghe TM. Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. *Hum Reprod Update*. 2013;19(5): 570-582.
144. Vicino M, Parazzini F, Cipriani S, Frontino G. Endometriosis in young women: the experience of GISE. *J Pediatr Adolesc Gynecol*. 2010;23(4):223-225.
145. Moore J, Copley S, Morris J, Lindsell D, Golding S, Kennedy S. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. *Ultrasound Obstet Gynecol*. 2002;20(6): 630-634.
146. Hudelist G, English J, Thomas AE, Tinelli A, Singer CF, Keckstein J. Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2011;37(3): 257-263.
147. Chapron C, Vieira M, Chopin N, et al. Accuracy of rectal endoscopic ultrasonography and magnetic resonance imaging in the diagnosis of rectal involvement for patients presenting with deeply infiltrating endometriosis. *Ultrasound Obstet Gynecol*. 2004;24(2):175-179.
148. Schreinemacher MH, Backes WH, Slenter JM, et al. Towards endometriosis diagnosis by gadofosveset-trisodium enhanced magnetic resonance imaging. *PLoS One*. 2012;7(3):e33241.
149. Manganaro L, Porpora MG, Vinci V, et al. Diffusion tensor imaging and tractography to evaluate sacral nerve root abnormalities in endometriosis-related pain: a pilot study. *Eur Radiol*. 2014;24(1):95-101.
150. Linnman C, Borsook D. Completing the pain circuit: recent advances in imaging pain and inflammation beyond the central nervous system. *Rambam Maimonides Med J*. 2013;4(4):e0026.
151. May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM. Peripheral biomarkers of endometriosis: a systematic review. *Hum Reprod Update*. 2010;16(6):651-674.
152. Vodolazkaia A, El-Aalamat Y, Popovic D, et al. Evaluation of a panel of 28 biomarkers for the non-invasive diagnosis of endometriosis. *Hum Reprod*. 2012;27(9):2698-2711.
153. Gargett CE, Schwab KE, Brosens JJ, Puttemans P, Benagiano G, Brosens I. Potential role of endometrial stem/progenitor cells in the pathogenesis of early-onset endometriosis. *Mol Hum Reprod*. 2014;20(7):591-598.
154. Brosens I, Gargett C, Gordts S, Brosens J, Benagiano G. Neonatal menstruation explains epidemiological links between fetomaternal conditions and adolescent endometriosis. *J Endometriosis Pelvic Pain Disord*. 2015;7(2):51-55.
155. Painter JN, Anderson CA, Nyholt DR, et al. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. *Nat Genet*. 2011;43(1):51-54.
156. Uno S, Zembutsu H, Hirasawa A, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. *Nat Genet*. 2010; 42(8):707-710.
157. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2014;3:CD009590.
158. Duffy JM, Arambage K, Correa FJ, et al. Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev*. 2014;4: CD011031.
159. Abrao MS, Petraglia F, Falcone T, Keckstein J, Osuga Y, Chapron C. Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management. *Hum Reprod Update*. 2015;21(3):329-339.
160. Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. *Hum Reprod*. 2014;29(10):2190-2198.
161. Georgievska J, Sapunov S, Cekovska S, Vasilevska K. Effect of two laparoscopic techniques for treatment of ovarian endometrioma on ovarian reserve. *Med Arch*. 2015;69(2):88-90.
162. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. *Hum Reprod Update*. 2011;17(3):327-346.
163. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia—an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2013;11:CD010567.
164. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2012;12:CD008242.
165. Giudice LC.Clinical practice. Endometriosis. *N Engl J Med*. 2010;362(25):2389-2398.
166. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344(11):783-792.
167. Deley MC, Ballman KV, Marandet J, Sargent D. Taking the long view: how to design a series of Phase III trials to maximize cumulative therapeutic benefit. *Clin Trials*. 2012;9(3): 283-292.
168. Flower A, Liu JP, Lewith G, Little P, Li Q. Chinese herbal medicine for endometriosis. *Cochrane Database Syst Rev*. 2012;5:CD006568.
169. Zhu X, Hamilton KD, McNicol ED. Acupuncture for pain in endometriosis. *Cochrane Database Syst Rev*. 2011;(9):CD007864.
170. Hou L, Chen M, Zhang CK, Cho J, Zhao H. Guilt by rewiring: gene prioritization through network rewiring in genome wide association studies. *Hum Mol Genet*. 2014;23(10):2780-2790.
171. Yavuz E, Oktem M, Esinler I, Toru SA, Zeyneloglu HB. Genistein causes regression of endometriotic implants in the rat model. *Fertil Steril*. 2007;88(suppl 4):1129-1134.
172. Xu H, Lui WT, Chu CY, Ng PS, Wang CC, Rogers MS. Anti-angiogenic effects of green tea catechin on an experimental endometriosis mouse model. *Hum Reprod*. 2009;24(3):608-618.
173. Ozcan Cenksoy P, Oktem M, Erdem O, et al. A potential novel treatment strategy: inhibition of angiogenesis and inflammation by resveratrol for regression of endometriosis in an experimental rat model. *Gynecol Endocrinol*. 2015;31(3):219-224.

174. Parazzini F, Vigano P, Candiani M, Fedele L. Diet and endometriosis risk: a literature review. *Reprod Biomed Online*. 2013; 26(4):323-336.
175. Hansen SO, Knudsen UB. Endometriosis, dysmenorrhoea and diet. *Eur J Obstet Gynecol Reprod Biol*. 2013;169(2):162-171.
176. Chiaffarino F, Bravi F, Cipriani S, et al. Coffee and caffeine intake and risk of endometriosis: a meta-analysis. *Eur J Nutr*. 2014;53(7):1573-1579.
177. Beste MT, Pfaffle-Doyle N, Prentice EA, et al. Molecular network analysis of endometriosis reveals a role for c-Jun-regulated macrophage activation. *Sci Transl Med*. 2014; 6(222):222ra16.
178. Meuleman C, Tomassetti C, D'Hoore A, et al. Clinical outcome after CO(2) laser laparoscopic radical excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis. *Hum Reprod*. 2011; 26(9):2336-2343.
179. Meuleman C, Tomassetti C, D'Hoore A, et al. Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. *Hum Reprod Update*. 2011;17(3):311-326.
180. Meuleman C, Tomassetti C, Wolthuis A, et al. Clinical outcome after radical excision of moderate-severe endometriosis with or without bowel resection and reanastomosis: a prospective cohort study. *Ann Surg*. 2014;259(3):522-531.
181. Meuleman C, Tomassetti C, D'Hooghe TM. Clinical outcome after laparoscopic radical excision of endometriosis and laparoscopic segmental bowel resection. *Curr Opin Obstet Gynecol*. 2012;24(4):245-252.
182. Eltigani EE. Childbearing in five Arab countries. *Stud Fam Plan*. 2001;32(1):17-24.
183. Adamson GD, Kennedy S, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. *J Endometriosis*. 2010; 2(1):3-6.