



MONASH University

**Early menopause: Implementation research
using the experiences and perspectives of
women and health professionals to translate
evidence into practice**

by

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BSc, MSc

A thesis submitted for the degree of
Doctor of Philosophy

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Notice 1

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General declaration for thesis including published works

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy, the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four manuscripts in total. Two original papers have been published in peer reviewed journals. Two other manuscripts have been submitted and are under review. The core theme of the thesis is needs analysis and evidence synthesis to inform translation of findings to development of evidence-based online resources. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia under the supervision of Clinical Associate Professor Amanda Vincent, Associate Professor Jacqueline Boyle and Professor Helena Teede.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of *chapters 2-4* my contribution to the work involved the following

Thesis Chapter	Publication Title	Status (published, in press, accepted or returned for revision)	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
2	Knowledge and attitudes of health professionals regarding menopausal hormone therapies	Published	70%, Literature review, data cleaning and analysis, interpretation of the results, and drafting the manuscript	Other authors, Amanda J Vincent , concept and design of the study, developed the protocol, interpretation of the results, and input into manuscript (20%) Jacqueline A Boyle , Contributed to study conception and design and input into manuscript (5%) Helena Teede , Contributed to study conception and design and input into manuscript (5%)	No No No
3	Effect of lifestyle modifications on cancer recurrence, survival and quality of life among gynaecological cancer women: A systematic review and meta-analysis	Published	75%, contributed to study design, systematic search, screening search results, data extraction and analysis, risk of bias assessment, and drafting the manuscript.	Cheryce Harrison , 15% contributed to data extraction and risk of bias assessment and input into manuscript. Other authors , 10% Amanda J Vincent , contributed to study design, and input into manuscript. Helena Teede , Input into manuscript. Jacqueline A Boyle , provided clinical expertise and supervision, input into manuscript	No No No No
3	Menopause Guideline appraisal and algorithm development for Premature Ovarian Insufficiency	Returned for revision and re-submitted	80%, contributed to systematic search and screening search results, guideline review, data extraction, data analysis and drafting the manuscript.	Other authors, 20% Jacqueline A Boyle , Contributed to study design, guideline review and input into manuscript Anna Wood , Contributed to guideline review and data extraction Helena Teede , Contributed to study design, and input into manuscript Amanda J Vincent , Contributed to study conception and design, guideline review, data extraction and input into manuscript	No Yes No No
4	Development and evaluation of an early menopause question prompt list	Accepted	75%, contributed to literature review, patient recruitment, data collection and analysis, thematic analysis and drafting the manuscript.	Nadia N Khan , 10% Contributed to thematic analysis, input into manuscript Other authors, 15% Jacqueline A Boyle , Provided clinical expertise and supervision, input into manuscript Melanie Gibson-Helm , Contributed to study design and input into manuscript Helena Teede , Contributed to input into manuscript Amanda J Vincent , Contributed to study conception and design, provided clinical expertise and supervision and input into manuscript	No No No No No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Summary

Early menopause (EM) (menopause before age 45 years) and premature ovarian insufficiency (POI) (<40 years) (1) can occur spontaneously or secondary to medical treatments. EM/POI is associated with significant morbidity, increased mortality and impaired quality of life (QoL) (1). Available evidence indicates a lack of women's and health professionals' (HPs) knowledge regarding EM/POI that could be a major barrier to early detection and appropriate treatment (2-4). Consumer preferences and wide internet accessibility support the use of online resources, however, current menopause websites are limited (5).

This research program aims to: i) explore women and HPs information needs and knowledge gaps regarding EM/POI, ii) systematically appraise evidence and current menopause clinical practice guidelines (CPGs), and iii) co-develop online EM/POI resources for women and HPs. Needs analysis and evidence synthesis have been undertaken to inform translation of findings to development of evidence-based website resources.

Chapter one of this project describes an introduction to EM/POI including definition, symptoms, diagnosis, health impacts and management. It also discusses women's and HPs' knowledge gaps regarding EM/POI and the potential role of the online resources on enhancing knowledge, health behaviour, risk perception and health outcomes.

Chapter two focuses on women's and HPs' information needs regarding EM/POI and e-health resources via two cross sectional studies. Here I report HPs' knowledge gaps regarding menopause management and variations in prescribing practices. I also determined that women with EM/POI are supportive of a comprehensive co-designed EM/POI eHealth website with multiple features. These findings informed development of online resources such as a question prompt list (QPL).

The first part of chapter three focuses on evidence synthesis through a systematic review of randomized controlled trials (RCTs) to assess whether lifestyle interventions can prevent cancer recurrence and improve overall survival and QoL in gynaecological cancer (GC) survivors and demonstrates that there is limited high-quality evidence addressing this question. This study also indicates that lifestyle modification does not improve QoL domains. The second part of chapter three presents a systematic evaluation of the content and methodological quality of current menopause CPGs using the AGREE (Appraisal of Guidelines for Research & Evaluation) tool II. Here I report significant limitations identified in the quality of the guidelines with only two guidelines assessed as high quality. Guidelines also vary in regard to the content and details of recommendations. Findings of this study informed development of a menopause management algorithm.

Chapter four of this project focuses on website and resource co-development with two components; one for women and one for HPs. The EM/POI website, developed in association with Healthtalk Australia, includes: (i) women's and HPs' experiences related to EM/POI (conducted with our research collaborators), (ii) comprehensive information about EM/POI and treatment options, (iii) EM QPL, (iv) EM/POI management algorithms, (v) links to other websites.

The website components including a QPL and management algorithm were co-developed using the information from chapter two and three of this project. Interviews of women with EM/POI and QPL pilot-testing in the clinic indicates that the EM QPL is an acceptable and feasible tool to use during medical consultations. The EM/POI management algorithms were developed from the CPG appraisal. The first version of management algorithms was refined using HPs' feedback.

This project demonstrated women's information needs and HPs' knowledge gaps regarding menopause management. It also highlights paucity of high-quality evidence on treating EM/POI that emphasizes the need for further research. By increasing evidence-based understanding of EM/POI, this research will enhance women and HPs interactions and EM/POI diagnosis / management leading to improved patient empowerment and health care.

Thesis by publication and PhD journey

Doctoral students at Monash University are encouraged to submit a thesis by publication, which includes papers that have been published, accepted, or submitted for publication. The papers can be inserted in their published format and may have more than one author. The thesis must reflect a sustained and cohesive theme, and brief framing or linking text is usually required to introduce and link the chapters and manuscripts.

This thesis contains a total of 5 chapters and 4 manuscripts. Two manuscripts have been published and the remaining two have been submitted and are under review. These manuscripts make up most parts of the chapters 2 to 4. I have collaborated with two other studies related to EM/POI during my candidature. The manuscripts have been submitted and are under review (I am co-author in these two papers). These manuscripts are included as an appendix.

Prior to commencing my PhD, I completed an undergraduate Bachelor degree in Midwifery and a Master degree (postgraduate course work and research) in Midwifery with a focus on maternal and child health. In 2007, I was employed as a researcher in a Reproductive Biomedicine Research Institute. I was involved in different research projects on infertility and IVF including RCTs and observational studies. In 2016, I decided to pursue a PhD to enhance my research skills and knowledge in the women's health and translational research.

This research program involved a high quality collaborative, co-designed translation project regarding the development of resources for a novel EM/POI website for women and HPs. This has required me to develop multiple research skills including conducting (i) needs analysis, comprising quantitative and qualitative studies involving women with EM/POI and HPs, and (ii) evidence synthesis, involving systematic reviews and AGREE clinical guideline appraisal. During my candidature, I also advanced my previous statistical knowledge by completing formal coursework in regression Methods for Epidemiology.

Acknowledgements

“This research was supported by an Australian Government Research Training Program (RTP) Scholarship.”

This journey would not have been possible without the support of my supervisors and family.

I would like to express my deepest gratitude to my supervisor Associate Professor Amanda Vincent for her sincere guidance, valuable advice and for always being accessible and making time to support me. I am indebted to her for encouraging me to present this project in multiple professional conferences which was a great experience for me. Her professional and meticulous comments were always enormous help and without her guidance and persistent help this thesis would not have been possible.

My heartfelt appreciation goes to Associate Professor Jacqueline Boyle for her wonderful guidance and advice. Her supports in all aspects of the project were invaluable. I have greatly benefited from her constructive comments and warm encouragement throughout my PhD journey.

I also express my gratitude to Professor Helena Teede for her generous support, valuable guidance and the opportunities I was given to conduct my research at MCHRI. She has been a great supervisor to advance my research and other professional skills which are helpful for my future endeavours.

My special thanks to Mr. Sanjeeva Ranasinha who provided us statistical advice and support throughout this project.

I am grateful to all of those who contributed to this project for designing and development of the EM/POI website particularly Associate Professor Renata Kokanovic, Dr. Kate Johnston-Ataata and Dr. Jacinthe Flore. A special thanks to Dr. Kim Huynh for assistance in patient recruitment and all research-related matters. My sincere appreciation to the health professionals who provided feedback on the menopause management algorithm and EM QPL.

I appreciate the co-authors for their intellectual input and cooperation in conducting the research presented in this thesis and finally, I would like to acknowledge all the volunteers who took part in the studies presented in this thesis. Thank you for your time and commitment,

this research would not have been possible without your participation. Your contribution have been a great help in informing the development of the online resources.

To my family, thank you for encouraging me in all of my pursuits and inspiring me to follow my goals. I am thankful to my mother and late father whose love and guidance are with me for everything I pursue.

Most importantly, I wish to thank my loving husband, Alireza for his amazing support and encouragement throughout this journey, and my two wonderful children, Helia and Arvin, who provide unending inspiration.

The work presented in this thesis was carried out at the Monash Centre for Health Research and Implementation (MCHRI), Faculty of Medicine, Nursing, and Health Sciences at Monash University. This research was supported by an Australian Postgraduate Award (APA) Scholarship and received funding from a National Health and Medical Research Council (NHMRC) Partnership project.

List of abbreviations, terms and definitions

AGREE	Appraisal of Guidelines for Research & Evaluation
CVD	Cardiovascular disease
EM	Early menopause
GC	Gynaecological cancer
GP	General practitioner
HP	Health professional
MHT	Menopausal hormone therapy
NHMRC	National Health and Medical Research Council
OCP	Oral contraceptive pill
POI	Premature ovarian insufficiency
QPL	Question prompt list
QoL	Quality of life
RCT	Randomized controlled trial
WHI	Women's Health Initiative

List of tables and figures

Table 1. Causes of premature ovarian insufficiency (chapter 1).

Figure 1. Implementation research summary plan (chapter 1).

List of publications

Listed below are the candidate's first-author and co-authored publications that are relevant to the period of candidature.

- **Yeganeh L**, Boyle J, Teede H, Vincent A. Knowledge and attitudes of health professionals regarding menopausal hormone therapies. *Climacteric: the journal of the International Menopause Society*. 2017; 20: 348-55.
- **Yeganeh L**, Harrison C, Vincent AJ, Teede H, Boyle JA. Effects of lifestyle modification on cancer recurrence, overall survival and quality of life in gynaecological cancer survivors: A systematic review and meta-analysis. *Maturitas*. 2018; 111: 82-9.
- **Yeganeh L**, Boyle JA, Wood A, Teede H, Vincent AJ. Menopause Guideline appraisal and algorithm development for Premature Ovarian Insufficiency. Returned for revision and resubmitted- *Maturitas*. 2019.
- **Yeganeh L**, Khan NN, Boyle JA, Gibson-Helm M, Teede H, Vincent AJ. Development and evaluation of an early menopause question prompt list. Accepted- *Menopause*. 2019.

Additional peer-reviewed publications during the candidature

Listed below are the candidate's other co-authored publications that are relevant to the period of candidature where the candidate has a contribution and where these relate to, but are not vital to, the core theme of the thesis.

Kulkarni M, **Yeganeh L**, Vollenhoven B, Vincent AJ. Complementary and Alternative Medicine (CAM) use in women with Primary Ovarian Insufficiency. *Submitted to "Complementary Therapies in Medicine"*.
(Appendix 3)

Kiriakova V, Cooray SD, **Yeganeh L**, Somarajah G, Milat F, Vincent AJ. Management of bone health in women with premature ovarian insufficiency: Systematic appraisal of clinical practice guidelines and algorithm development. *Maturitas*. 2019, 128: 70-80.
(Appendix 4)

List of conference presentations

Listed below are the candidate's conference posters and presentations regarding research included in this thesis. The presenting author's name is underlined.

Oral presentations

1. Yeganeh L, Boyle J, Ranasinha S, Teede H, Vincent A. Health professionals' knowledge regarding menopause and menopausal therapies. **Australasian Menopause Society** - Fremantle, Western Australia - 2016.
2. Yeganeh L, Boyle J, Ranasinha S, Teede H, Vincent A. Attitudes of health professionals towards menopausal hormone therapies. **Australasian Menopause Society** - Fremantle, Western Australia - 2016.
3. Yeganeh L, Boyle JA, Wood A, Teede H, Vincent AJ. Appraisal of clinical practice guidelines of menopause management using AGREE II instrument to inform the development of an early menopause/premature ovarian insufficiency management algorithm. **International Menopause Society** - Vancouver, Canada - 2018.

Poster presentations

1. Yeganeh L, Harrison C, Vincent AJ, Teede H, Boyle JA. Effects of lifestyle modification on cancer recurrence, overall survival and quality of life in gynaecological cancer survivors: A systematic review and meta-analysis - **Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)** - Auckland, New Zealand - 2017.
2. Yeganeh L, Vincent, AJ, Gibson-Helm, M, Teede, H, Boyle, JA. Women's perceptions regarding early menopause e-Health resources to facilitate self-care. **The European Society of Human Reproduction and Embryology (ESHRE)**-Barcelona, Spain - 2018.
3. Yeganeh L, Boyle J, Gibson-Helm M, Teede H, Vincent AJ. Developing an early menopause question prompt list: women's information needs. **International Menopause Society** - Vancouver, Canada - 2018.

Additional conference presentations during candidature

1. Vincent AJ, Yeganeh L, Gibson-Helm M, Teede H, Boyle J. Women's perspectives of early menopause: development of a Word cloud. **International Menopause Society** - Vancouver, Canada - 2018.

2. Kiriakova V, Cooray SD, **Yeganeh L**, Somarajah G, Milat F, Vincent AJ. Premature Ovarian Insufficiency/Osteoporosis clinical practice guideline systematic review. **Endocrine Society of Australia** - Adelaide, Australia - 2018.

List of awards and prizes

Year	<i>Award / prize</i>
2018	Travel grant to present at the International Menopause Society congress-Monash university
2017	Travel grant to present at the RANZCOG congress-Monash University
2017	Australian Menopause Society award for the best peer-reviewed publication
2016	Jean Hailes prize for the best oral presentation
2016	Travel grant to attend Australasian Menopause Society congress-Monash University

Scholarship and funding

Year	<i>Scholarship / funding</i>
2016	Australian Menopause Society scholarship
2016	Australian postgraduate award scholarship-Monash University

Coursework and short courses completed

Year	<i>Coursework / short course</i>
2017	Regression methods for epidemiology
2016	Ethics and Good Research Practice
2016	Systematic review, meta- analysis and risk of bias assessment
2016	Introduction to STATA
2016	Qualitative research methods for public health
2016	Induction modules
2016	Introduction to Biostatistics & Epidemiology (Exempted)
2016	Conference presentation

Statement of aims

Overall aim

Overall, the body of work presented in this thesis aims:

- To undertake needs analysis, evidence synthesis and translation related to EM/POI to support the development of an evidence-based educational website for women and HPs

Chapter 2: Needs Analysis

This chapter presents two cross-sectional studies on women and HPs which aims:

- To evaluate the knowledge and attitudes of Australian HPs including general practitioners (GPs), gynaecologists and endocrinologists, to menopausal hormone therapy (MHT).
- To explore information and communication needs of women with EM/POI to inform the development of an EM QPL

Chapter 3: Evidence Synthesis

This chapter focuses on evidence synthesis through two systematic reviews aiming:

- To determine whether lifestyle interventions can prevent cancer recurrence and improve overall survival and QoL in endometrial and ovarian cancer survivors.
- To systematically search and evaluate the quality of menopause management CPGs

Chapter 4: Translation with Health resource development

This chapter presents translation of evidence into development of EM/POI online resources.

Specific aims are:

- To develop and evaluate an EM QPL to facilitate women-HPs interactions.
- To develop a management algorithm to assist clinical diagnosis and management of women with EM/POI

Chapter 1: Introduction to early menopause or premature ovarian insufficiency

1.1. Definition, prevalence and causes

EM is defined as menopause occurring before the age of 45 years or more specifically between 40- 45 years and affects over 10% of women (1, 6). POI refers to loss of ovarian function before age 40 years and occurs in approximately 1% of women (6). Due to increasingly longer life expectancies, women with EM/POI may spend a significant part of their lifespan in the postmenopausal stage (7). EM/POI can occur spontaneously or following medical interventions (1). As the number of breast and GC survivors in women of reproductive age are increasing, more women are facing menopause as a consequence of their cancer treatment (8, 9).

Various factors can influence the timing of menopause including genetic (chromosome abnormalities, gene mutations and a strong family history), autoimmune diseases, infections or iatrogenic causes (Table 1) (10-12). Medically induced menopause occurs following bilateral-oophorectomy or other cancer treatments such as chemotherapy or radiotherapy (1), although the risk of EM/POI depends on the age of the woman, type, duration and dose of chemotherapy or radiotherapy. However, in a large percentage of women the cause of EM/POI cannot be identified.

Table 1: Causes of premature ovarian insufficiency

Causes	Frequencies	References
Genetic	10%-13%	(13-17)
Chromosome abnormalities (monosomy X; X chromosomal mosaicism, X deletions, X-autosome translocations, X-isochromosomes and other rearrangements)		
Gene mutations (Fragile X mental retardation 1 (FMR1))		
Autoimmune disease	5%	(18)
Thyroid		
Adrenal		
Coeliac		
Infections	2-8%	(19)
Iatrogenic	11%	(20)
Chemotherapy		
Radiotherapy		
Pelvic surgery		
Bilateral oophorectomy		
Idiopathic	42%	(21)

Note: the frequencies vary depending the source of the population.

1.2. Health impacts

EM/POI is associated with negative psychological and physical effects with the most significant impacts on health-related QoL (22-24). Women with EM/POI may experience a range of symptoms that are usually similar to those who proceed through natural menopause (25). Vasomotor symptoms including hot flushes and night sweats are the most common symptoms of EM/POI that are related to estrogen deficiency and may occur gradually or suddenly (25). Women may also be affected by sleep disorder, tiredness, psychological distress and urogenital dysfunction including vaginal dryness, dyspareunia and loss of libido (24, 26). However, the frequency and severity of menopausal symptoms may vary with the cause of EM/POI (2).

Early loss of ovarian function, whether spontaneous or induced, is associated with multiple health risks and mortality (27). Earlier cross-sectional studies reported that the symptoms and side effects of estrogen deficiency are more severe in women with EM/POI than when menopause occurs gradually at a natural age (28). Women who experience EM/POI are at higher risk of osteoporosis (29) and bone fractures (30). Observational data also suggests a potential association between earlier age at menopause and increased risk of cognitive impairment, Alzheimer's disease, Parkinson's disease and diabetes mellitus (31-36). A large cohort study with long-term follow-up reported a 2.7% mortality related to neurological disorders in young women who underwent bilateral oophorectomy and the rate was similar to those who were treated with estrogen (37). However, the beneficial effects of MHT on cognitive function of women with natural menopause has been also demonstrated in double-blind placebo-controlled studies (38, 39). Similarly, previous studies showed improved verbal memory and cognitive function in surgically menopausal women using MHT (40, 41).

Early onset of EM/POI may be also associated with an increased risk of type II diabetes mellitus due to the early cessation of the protective effects of endogenous estrogen (33). Evidence indicates a strong link between untreated EM/POI and an increased risk of coronary heart disease (CHD), cardiovascular disease (CVD) mortality and overall mortality (27, 42-44). The rate of CVD mortality following bilateral oophorectomy in women under 45 years was reported 8%, although this rate was reduced to 3.3% in women who were treated with estrogen (45). Prospective cohort studies indicate that combined MHT may restore endothelial dysfunction (46) and reduce the risk of ischemic heart disease in POI women (47). However, a recent systematic review indicates limited evidence regarding the effect of hormone therapy on bone and cardiovascular health and QoL in women with EM/POI (48).

Women with EM/POI may have an increased risk of depression and anxiety (49), low self-esteem, lower perceived social support and decreased physical and overall psychological wellbeing, highlighting the need for psychological support (6, 50-52). EM/POI may also have

significant negative impacts on sexuality and intimacy leading to long-term sexual issues if untreated (50). Sexual dysfunction following EM/POI can develop due to factors including physiologic hormonal deprivation and psychological effects (53). EM/POI may also impact partners and families (54).

1.3. Diagnosis and management

Australian and international studies indicate that the diagnosis of EM/POI is often difficult and can be delayed, putting women at risk of physical and psychological morbidities and may contribute to sub-optimal management (3, 55, 56). Preventive and management strategies need to be started upon EM/POI diagnosis. However, women's and HPs' knowledge gaps regarding menopause, perceived women concerns about the potential risks of MHT, paucity of high-quality evidence and variations in prescribing practices are reported as major barriers to early diagnosis and treatment (4, 57).

Several management strategies are considered for EM/POI based on women's preferences, co-morbidities and needs, including MHT, non-hormonal treatment and lifestyle management (6). MHT is the most effective treatment to relieve vasomotor symptoms and prevent or ameliorate the associated health risks (see previous section). This therapy is generally recommended with early initiation and at least until the average age of natural menopause (~50 years) (6, 12). However, following publication of the Women's Health Initiative (WHI) study in 2002 (58), concerns have been raised about the risks/benefits of MHT. The results of the WHI randomized, controlled trial of combined MHT in 2002 was announced as indicating a 26% increase in breast cancer and not surprisingly, received worldwide attention (58). The breast cancer risk was actually a relative risk of HR 1.25 (1.07-1.46 nominal CI) which was not significant when fully adjusted with a reported HR 1.25 (0.83-1.92 CI) (59). The results of the estrogen-only arm of the WHI published in 2004 showed a non-significant reduction in breast cancer after 7 years of estrogen-alone HRT (60). It was also announced that MHT increased the risk of CVD (60). In contrast to the initial announcement, a further analysis by the same investigators in 2007 stated no significant increases in risk due to hormone therapy and a reduction in total mortality at ages 50 – 59 years (and received no media attention) (61). In a recent study by Manson and colleagues, no increase in all-cause or specific mortality was observed among women who have used combined MHT or estrogen-only MHT for 5-7 years compared to the placebo group over a cumulative 18 years follow-up (62). The initial reporting and interpretation of the results led to insecurity and concerns among women and HPs with variable resolution as subsequent publications emerged (63-65).

Although, WHI involved women aged over 50 years with an average of 63 and is not directly relevant to POI as baseline risk and impact of MHT may vary according to the two populations.

When there are concerns or contraindications over using MHT (eg. estrogen sensitive cancers), non-hormonal therapies such as selective serotonin reuptake inhibitors (SSRIs), serotonin nor-epinephrine reuptake inhibitors (SNRIs), gabapentin, and clonidine are effective alternatives to relieve vasomotor symptoms; however, these have mainly been studied in post-menopausal women aged over 50 years (66). There is conflicting evidence regarding the safety and efficacy of complementary medicines/therapies which has complicated EM/POI management (6, 67, 68).

1.4. Knowledge gaps and unmet information needs

Women's and HPs' knowledge gaps regarding EM/POI potentially contribute to delayed diagnosis, sub-optimal management, variation in care, poor risk perception, non-compliance with treatment and poor health outcomes (2, 4, 69, 70). Evidence indicates a strong association between health literacy, behaviour change and improved health outcomes (71). Therefore, raising women's and HPs' awareness regarding menopause management and enhancing evidence-based practice to reduce prescribing variations is crucial to improve health outcomes. Educational health resources have been reported as an efficient means of raising women's and HPs' awareness that can improve self-management, optimize health-related behaviours, promote informed decision making and improve outcomes (72-74).

1.5. Online Health resources

Provision of evidence based information and resources are integral to high quality collaborative patient centred care, improved patient experience, promotion of best practice and optimal health outcomes (73, 74). In an observational pilot-study, women who experienced premature menopause reported the internet as the best source of health information (75). Co-development of an evidence based website including novel resources such as QPLs provides a valuable medium enhancing HPs' knowledge and consistencies in care, addressing women's needs and will potentially improve patient empowerment, knowledge, risk perception, health behaviour and shared decision-making at both the individual and community level (73).

A comprehensive web-based resource offering information regarding EM/POI can therefore promote both self-management and patient-HP interaction and potentially enhance clinical care and health outcomes, including QoL. However, to date there is not any website specifically for women and HPs involved in clinical care of EM/POI, and the existing menopause consumer websites have substantial limitations in quality and content information which limits their usefulness (5, 76, 77).

1.6. Outline of the thesis

This research project will identify and address knowledge gaps in women and HPs with regard to EM/POI through needs analysis (quantitative and qualitative research), evidence synthesis (systematic reviews) and CPGs review. This body of work guides translation of findings to inform the development of resources for a novel evidence-based EM/POI website in order to improve health outcomes.

To address these objectives, the following studies were undertaken:

1. Needs analysis: The first part of this thesis involves two cross-sectional studies assessing consumers and HPs knowledge and information needs regarding EM/POI management.
2. Evidence synthesis: This component of my PhD studies focuses on evidence synthesis, in which I conducted a systematic review and meta-analysis assessing the effect of lifestyle modifications on cancer survival, recurrence and QoL among GC survivors. I also led a systematic appraisal of evidence and menopause CPGs to assess their methodological and content quality.
3. Translation and Resource Development: The findings from the HP survey and systematic reviews informed the development of the algorithms for diagnosis and evaluation of EM/POI and menopause management. The findings from the women survey informed the development of an EM QPL. This was followed by a qualitative study involving individual and focus group interviews to refine the QPL and a subsequent pilot study to assess the acceptability and feasibility of the QPL.

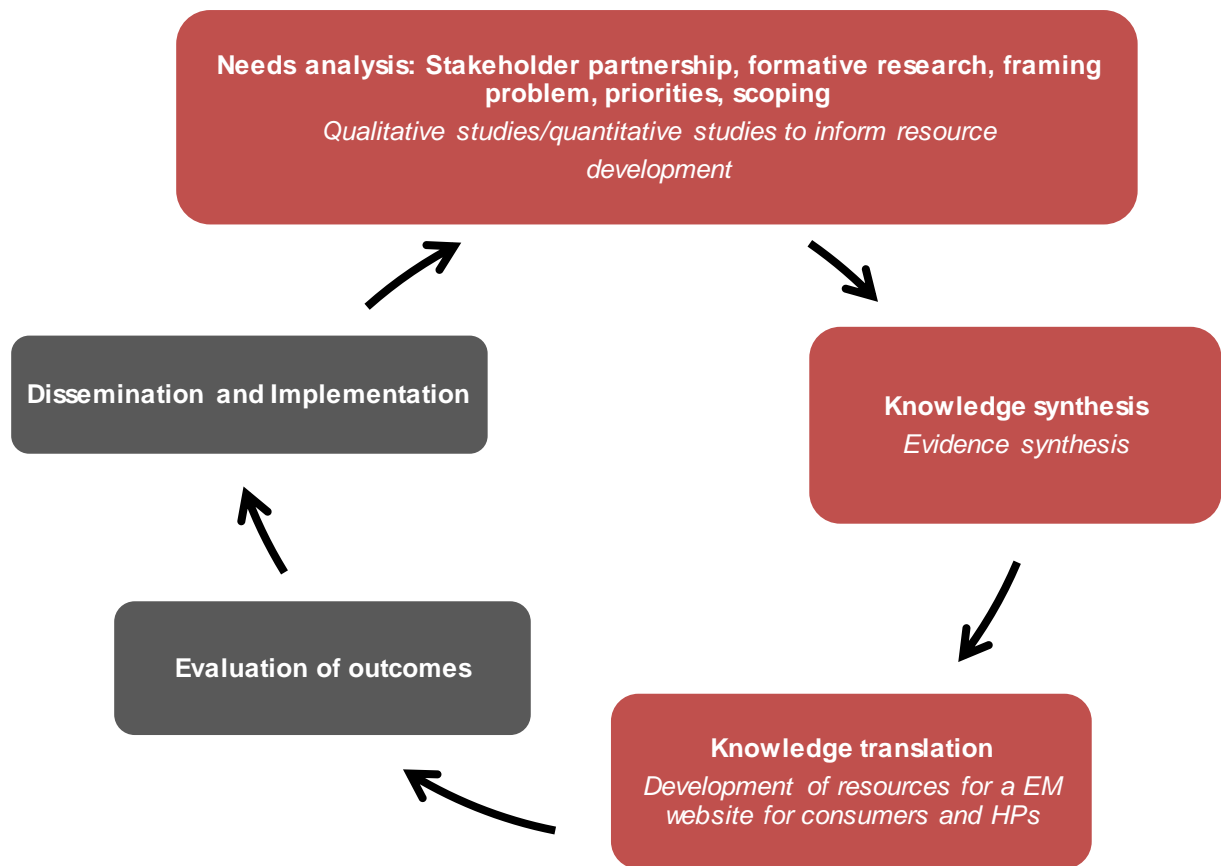


Figure 1. Implementation research summary plan

Note: Components my work relate to are shown in red colour

Chapter 2: Needs Analysis

2.1. Introduction

Providing accurate information about a range of health conditions is widely recognised as one of the most important components of effective care that assist decisions on when to seek healthcare and what to ask healthcare providers (78). Evidence suggests that women want to be fully informed regarding different aspects of their condition and actively engaged in their healthcare (79). However, surveys of women with POI indicate that they are generally dissatisfied with the information and supports provided by HPs suggesting inadequate awareness of HPs regarding women's information needs (75, 80, 81).

HPs' knowledge gaps may contribute to women with EM/POI, receiving differing treatments depending on the type of HPs consulted. Indeed, breast surgeons and GPs seemed more likely to prescribe combined MHT to women with EM after breast cancer compared to other specialties (57). Also, recommendations from international societies (6, 12), is that MHT be continued until at least the average age of menopause in women with EM/POI. However, there is evidence, although limited, that clinicians may not comply with these recommendations. In a previous study, to identify diagnostic patterns, frequency of appropriate MHT, obstetric outcomes, fertility treatment and counselling of women with fragile X POI, 23 out of 79 women with POI reported that their clinician never recommended HRT or advised them against using hormone therapy (56). In our study of Australian clinicians, almost 20% of clinicians reported that the duration of MHT in women with premature menopause should be less than 10 years. There is limited evidence for women with EM due to other causes but these two studies (56, 57) highlight the importance of identifying HPs knowledge gaps or misunderstandings regarding EM/POI management to assist HPs to better address women's needs.

Understanding of menopausal therapies and health related behaviours varies across women experiencing POI due to different causes; consequently, women may be unable to make informed decisions regarding their treatment options (2). In fact, more women with induced menopause than spontaneous menopause perceived that hormone therapy may increase the risk of breast cancer (2). Over 50% of women with POI never used MHT, started it years after diagnosis or failed to continue the recommended replacement up to the average age of menopause (56, 82).

Most women have limited understanding of EM/POI at the time of diagnosis and require appropriate information to empower them to cope with the decisional conflicts (83). However, women report that their information needs are not adequately met particularly regarding long-term menopause implications and menopause management (81, 83, 84). This may contribute

to feelings of distress, a lack of adherence with therapy and dissatisfaction with the healthcare experience (69).

An understanding of the information needs of women affected by a chronic condition would provide a basis to develop strategies that facilitate self-acquisition of knowledge and empower women to communicate their information needs to HPs (72). This chapter explores (i) consumers' information needs regarding EM/POI and (ii) HPs knowledge gaps regarding menopause including specific questions related to EM/POI regarding MHT indications, duration and prescribing habits, through two cross-sectional studies to inform the development of online resources.

2.2. Consumer survey to explore information needs of women with EM to inform the development of an EM QPL

Findings from this study are presented as an abstract (shown below) and informed the co-development of a novel EM QPL (included in the manuscript presented in Chapter 4).

The consumer survey and two posters related to this study which were presented at the International Menopause Society (IMS) and ESHRE conferences are available as appendix 1.

Summary

This study involved a consumer survey to explore perspectives and information needs of women with EM to inform the development of an EM QPL. A broad range of women with a diagnosis of EM were recruited from the clinic or the community and invited to complete an online or paper survey. Data related to demographics, medical history, e-resource use, support for an App, desired features of the ideal App, perceptions regarding communication difficulties, QPL use, topics to include in a website, fact sheet, QPL or App and “What words associate with EM?” were collected. Women reported difficulty communicating with HPs regarding vaginal/urinary symptoms, psychological effects and sexual function. Most women would be likely to use an EM QPL during consultations and considered a QPL as useful to include in an EM website. A majority of women considered diagnosis, symptoms, physical/psychological effects, long term implications, hormonal/non-hormonal management and lifestyle changes very important/essential to include in a QPL. The findings of this study underpin the website content and resource development.

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P-650 Women's perceptions regarding early menopause eHealth resources to facilitate self-care

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Study question: What are women's needs and perspectives regarding early menopause (EM) eHealth resources?

Summary answer: Most women with EM have access to multiple electronic devices and are supportive of a comprehensive co-designed EM eHealth web-site or App with multiple features.

What is known already: Provision of evidence based information and resources are integral to high quality collaborative patient centred care, improved patient experience, promotion of best practice and optimal health outcomes. Consumer and health professional knowledge gaps regarding EM exist and potentially contribute to the observed delayed diagnosis, variation in management, dissatisfaction with care, non-compliance with cancer treatment, poor risk perception and poorer outcomes. With continuing increases in digital device ownership, women are seeking electronic resources to facilitate knowledge access and enhance self-health management, yet current EM related eHealth resources are either lacking or are inadequate for women's needs.

Study design, size, duration: A cross-sectional study of 386 Australian women with EM recruited between May and November 2017. The study was approved by the Monash Health Human Research Ethics Committee.

Participants/materials, setting, methods: Women with a self-reported diagnosis of EM, recruited from hospital clinics or the community, completed an online or paper survey. Exclusion criteria were no formal EM diagnosis or non-Australian residence ($n = 123$). Data collection included: demographics, medical history, current use of electronic resources to manage health/EM, support for an App, desired features of the ideal App and EM information topics. Data analysis included descriptive statistics (mean \pm standard deviation) and logistic regression.

Main results and the role of chance: Of 263 women, the mean age was 53.81 (± 10.68) with EM diagnosed at age 38.54 (± 5.27). Most participants were diagnosed with EM ≥ 5 years ago (78%), lived in metropolitan areas (55%) and had post-school qualifications (71%). Reported cause of EM was surgical removal of ovaries (30%), unknown (29%), cancer therapy (26%), or autoimmune/genetic/metabolic (14%). Most women had a smartphone (84%) and 98% of those owned multiple electronic devices. Women reported they would prefer a website (59%) to an App (38%) to manage EM with only 37% reporting current App use to manage health and 2% to manage EM. However, 67% women thought an App would be helpful and 45% would be likely to use it. Future menopause App use was less likely with increasing age (OR, 0.96; CI, 0.93-0.99, $p = 0.008$) but there were no significant associations with residential location, education, time since diagnosis, or cause of EM. Features considered very important/essential to include in an EM App were: evidence-based information (81%), question prompt list (78%), opportunities to ask an expert (76%) and ability to record symptoms/ health measures (67%). EM topics rated very important/essential to include ($>80\%$ respondents) were: diagnosis, symptoms, physical/psychological effects, long term implications, hormonal/non-hormonal management and lifestyle changes.

Limitations, reasons for caution: Potential response bias in relation to age/self-reported diagnosis of EM. These findings may be less relevant to non-English speakers, women with lower literacy/ educational attainment and those without internet access.

Wider implications of the findings: The results of this study will help development of high quality eHealth resources aiming to improve self-care and health outcomes. Further research is required to address limitations, and co-develop resources, including user testing and evaluation.

Trial registration number: Not applicable.

2.3. Knowledge and attitudes of health professionals regarding menopausal hormone therapies.

Summary:

This study involved a survey of Australian HPs regarding self-reported knowledge and attitudes regarding the management of menopause including EM. We identified that HPs have knowledge gaps regarding EM management which vary with specialty. Specifically we revealed that HPs reported vasomotor symptoms as the main indication for oestrogen therapy in women with EM/POI with osteoporosis prevention the second most frequently reported indication. OCPs were reported as the preferred systemic therapy for women with EM/POI and would be recommended by most HPs until the average age of natural menopause. However, variation was observed between specialties regarding duration of therapy; a greater proportion of endocrinologists advised a longer duration. In contrast, transdermal MHT was recommended by most HPs, as the first-line therapy for symptomatic menopausal women aged over 50 years. Almost 50% of HPs reported limited knowledge of non-hormonal therapies which are indicated when MHT is contra-indicated. These findings indicate HP knowledge gaps and highlight the need for evidence-based information with implementation for HPs.

Yeganeh L, Boyle J, Teede H, Vincent A. Knowledge and attitudes of health professionals regarding menopausal hormone therapies. *Climacteric: the journal of the International Menopause Society* 2017 20 348-55.

Knowledge and attitudes of health professionals regarding menopausal hormone therapies

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ORIGINAL ARTICLE



Knowledge and attitudes of health professionals regarding menopausal hormone therapies

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ABSTRACT

Objective: To evaluate the knowledge and attitudes of Australian health professionals (HPs) including general practitioners (GPs), gynecologists and endocrinologists, to menopausal hormone therapy (MHT).

Methods: Participants were recruited from medical societies/colleges and a national GP conference. An online survey containing devised and previously published questions was used. Data analysis included frequencies, ANOVA, χ^2 and regression analysis.

Results: A total of 745/888 responses were analyzed. Fewer HPs (52%) reported being knowledgeable regarding non-hormonal therapies compared with menopause physiology or MHT (72%), with no significant knowledge differences between specialties. Most HPs (91%) would offer MHT to symptomatic menopausal women. The combined oral contraceptive pill (52%) was preferred for women with premature menopause. Transdermal MHT was preferred for women >50 years, although differences were observed between specialties ($p = 0.005$). HPs varied regarding duration of MHT for women with premature menopause ($p = 0.009$) and women over 50 years ($p = 0.001$). Menopause society members were more likely to prescribe MHT and for longer duration ($p < 0.05$). Consumer concern regarding breast cancer was considered the main barrier in prescribing MHT.

Conclusions: Although most HPs will recommend MHT, when indicated, for symptomatic menopausal women, variations exist between specialties in prescribing practices. HPs' knowledge gaps and perceived consumer concerns are barriers to prescribing MHT.

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Introduction

Women now spend about one-third of their lifespan in the postmenopausal stage or longer if premature menopause (menopause before age 40 years) occurs¹. Vasomotor symptoms are features of menopause^{2,3} that have the most significant impact on health-related quality of life⁴. MHT is the most effective therapy to improve quality of life by relieving menopause symptoms⁵. This therapy was widely used among postmenopausal women until 2002, but the attitudes of women and clinicians changed considerably following the publication of the Women's Health Initiative (WHI) study that concluded the harmful effects of MHT potentially exceeded the benefits⁶. This led to a decrease in clinicians' prescribing practices with women being less likely to use hormonal treatments and more inclined to use non-hormonal or non-government-approved treatments^{7–9}.

Consumers' lack of knowledge about menopause and MHT can lead to avoidance and early discontinuation of treatment¹⁰. HPs have a great role in improving patients' awareness about MHT and also treatment adherence¹¹. In a population-based study in Sweden, almost 70% of consumers were fully informed about MHT by physicians¹², and medical

advice has been the main factor improving adherence to treatment, particularly in low socioeconomic areas¹³. However, reports indicate HPs themselves have knowledge gaps regarding the potential risks and benefits of MHT¹⁴. Consequently, women may receive varying treatment strategies and recommendations depending on the type of specialist consulted¹⁵. Post-WHI evidence indicates that most HPs are reluctant to prescribe hormone therapy to menopausal women, particularly for preventative indications¹⁶. Conversely, many health-care providers remain unconvinced regarding the findings of the WHI trial, due to early cessation of the trial¹⁷.

Reappraisals of recent evidence, clinical trials and guidelines supporting MHT^{18–20} have raised questions about whether there has been a shift in HPs' views and practices. Most previous post-WHI reports on knowledge and practice assessed gynecologists outside Australia and, to date, there is no evidence assessing Australian HPs' knowledge, views and practices of MHT. Therefore, in the context of effective MHT, confusing WHI results and individual lack of knowledge, this study aimed to determine current Australian HPs' knowledge and attitudes to prescribing MHT, including indications and concerns over MHT. We also aimed to explore whether

differences exist between specialties including GPs, endocrinologists and gynecologists.

Methods

This study was approved by the Monash Health Human Research Ethics Committee. Self-administered online questionnaires were emailed to members of the Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG), the Australasian Menopause Society (AMS) and the Endocrine Society of Australia. GPs attending a national health education conference were also invited to participate. This study was conducted between October 2015 and February 2016. Individual societies/colleges distributed the initial email with a follow-up reminder 2 weeks later. GP attendees at the conference conducted on 24 October 2015 were provided with the online link to the survey. A total of 888 HPs responded and returned the questionnaires. Respondents who had non-medical degrees, trainees, HPs from outside Australia and those who did not work in clinical practice were excluded.

Data were collected using Survey Methods, an online survey software. The questionnaire included multiple-choice, yes/no, Likert-scale and open-ended questions. Completion and return of the survey indicated HPs' consent for participation in this study. The survey included questions derived from previous studies of HPs and menopause^{14,16,21–23}. The questionnaire was piloted by 12 HPs from the three specialty groups and the survey questions amended according to their feedback. The questionnaires consisted of three sections:

- (1) Related to demographic characteristics of HPs (age, gender, work place, medical specialty, years graduated from medicine, years practiced and membership of a menopause/endocrine society);
- (2) Questions measuring HPs' self-reported knowledge regarding menopause physiology, menopause management (MHT and alternative therapies), bone health, cardiovascular disease and metabolic syndrome. Clinicians were asked to assess their knowledge according to a five-point Likert scale ranging from very knowledgeable to know nothing; and
- (3) Questions regarding HPs' attitudes to menopause management. HPs were asked regarding their likelihood to prescribe MHT based on a five-point agree/disagree Likert scale, the preferred type and duration of treatment, indications of prescribing MHT according to age groups, contraindications of prescribing MHT (based on a five-point Likert scale ranging from very likely to very unlikely) and barriers that HPs experience during their practice.

Opinions of clinicians regarding the current guidelines and the preferred method of obtaining up-to-date information about MHT were also asked.

Calculation of sample size

The calculation of sample size was based on findings from a pilot study of clinicians' prescribing habits for women with

breast cancer, with the largest effect size of 3% versus 14%¹⁵. Assuming that level of significance was set at 5% and power at 80%, we needed 100 participants in each specialty group.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0. Continuous variables were analyzed using one-way analysis of variance (ANOVA) test and was reported as mean \pm standard deviation (SD). Categorical variables were analyzed by χ^2 test and reported as numbers/percentages. A logistic regression model was used to measure the association between independent variables such as age, sex, years graduated and membership of a menopause society with HPs' knowledge. We also used a logistic regression model to test the association between membership in a menopause society and the likelihood of prescribing MHT for potential indications/contraindications of MHT. Due to the small number of responses to some categories of Likert scale, we collapsed from five points to two or three points. The final collapsed groups were (knowledgeable vs. limited knowledge), (agree vs. neutral vs. disagree) and (likely vs. neutral vs. unlikely). A p value <0.05 was considered statistically significant.

Results

From 888 returned questionnaires, 745 were eligible for analysis. As this was an online survey and potential overlap could exist between members of the societies/college, the respondent rate was unable to be calculated. Most respondents were women and aged 41–60 years (Table 1). The mean (SD) years of graduation from medical degree and work experience were 26.28 ± 11 years and 20 ± 11.14 years, respectively. About 22% of the participants had membership of menopause societies including Australasian, International, North American, British and Irish Menopause Society (Table 1).

Almost 72% of HPs reported being knowledgeable regarding menopause physiology and MHT. However, only 52% of HPs reported being knowledgeable regarding non-hormonal therapy and 43%, 42% and 45% reported limited knowledge concerning bone, cardiovascular and metabolic health, respectively. No significant differences were observed between specialties (Table 2). Univariate logistic regression models were used to test the association of knowledge with demographic characteristics of HPs by age, time since graduation and membership of menopause society. Younger age was associated with knowledge regarding non-hormonal therapies (odds ratio (OR) 1.80; 95% confidence interval (CI) 1.12–2.90; $p = 0.01$).

There was also a trend toward increased knowledge regarding non-hormonal therapy in those who graduated more recently, but the association did not reach statistical significance (OR 1.42; 95% CI 0.99–2.04; $p = 0.05$). Membership of a menopause society was associated with a decreased likelihood of knowledge regarding menopause physiology (OR 0.62; 95% CI 0.42–0.92; $p = 0.02$), but no

Table 1. The basic characteristics of health professionals. Data are given as mean \pm standard deviation, or n (%). One-way analysis of variance (ANOVA) and χ^2 tests were used for comparison between groups.

Characteristics	Specialty			Total	p Value
	General practitioners (n = 283)	Endocrinologists (n = 61)	Gynecologists (n = 401)		
<i>Work place</i>					<0.001
Hospital-based	15 (5%)	25 (41%)	164 (41%)	204 (27%)	
Solo private/general practice	42 (15%)	6 (10%)	128 (32%)	176 (24%)	
Group private/general practice	212 (75%)	5 (8%)	52 (13%)	269 (36%)	
Mix	14 (5%)	25 (41%)	57 (14%)	96 (13%)	
<i>Age (years)</i>					0.05
≤ 40	59 (21%)	16 (27%)	66 (17%)	141 (19%)	
41–60	176 (62%)	29 (48%)	242 (61%)	447 (60%)	
>60	47 (17%)	15 (25%)	92 (23%)	154 (21%)	
<i>Gender</i>					<0.001
Male	72 (26%)	24 (39%)	191 (48%)	287 (39%)	
Female	210 (75%)	37 (61%)	209 (52%)	456 (61%)	
Number of years graduated	25.55 \pm 10.70	25.54 \pm 11.13	26.91 \pm 11.13	26.28 \pm 10.98	0.24
Number of years practicing	20.46 \pm 11.54	17.15 \pm 11.39	19.92 \pm 10.78	19.90 \pm 11.14	0.11
Member of a menopause society	70 (25%)	10 (17%)	79 (20%)	159 (22%)	0.17

significant association was observed for other demographics. After adjusting for all demographic variables, the association between younger age and years since graduation with knowledge remained significant, but not for other variables.

The majority of HPs (91%) would offer MHT to symptomatic menopausal women with no significant differences between specialty groups (Table 2). Combined oral contraceptive pills, as the preferred treatments for women with premature menopause, would be recommended until age 51 years by 58% of clinicians. Transdermal MHT was preferred by 52% of HPs for women >50 years, although variation was observed between specialties ($p = 0.005$) (Table 2). Combined MHT and estrogen-only MHT would be offered by 78% and 56% of HPs for 1–5 years for women >50 years, although 21% of HPs would offer estrogen-only MHT for 6–10 years and 17% prescribe indefinitely. Variation was seen between specialties regarding duration of combined MHT ($p = 0.001$) (Table 2).

Members of a menopause society were more likely to offer combined (OR 1.91; 95% CI 1.13–3.20; $p = 0.01$) and estrogen-only MHT (OR 3.81; 95% CI 2.41–6.03; $p < 0.001$) for longer term (6–10 years) rather than 1–5 years for women over 50 years. Most HPs reported that they would prescribe MHT for vasomotor symptoms in women with premature menopause (80%), women aged 50–55 years (85%) and women aged 56–60 years (62%) (Figure 1). Univariate logistic analysis showed that membership of a menopause society was associated with an increased likelihood to prescribe MHT in a setting of potential indications and contraindications (Tables 3 and 4).

Personal histories of venous thrombosis (86%), breast cancer (85%), cerebrovascular disease (70%), uterine cancer (69%) and ischemic heart disease (62%) were the main concerns of clinicians in prescribing MHT. About 45% of HPs would not recommend MHT for women who have concerns about breast cancer. There were variations by specialty for prescribing MHT for some potential contraindications, including personal history of venous thrombosis ($p < 0.001$), cerebrovascular disease ($p = 0.003$), ischemic heart disease ($p = 0.03$), hyperlipidemia ($p = 0.006$), hypertension ($p = 0.04$), diabetes ($p = 0.01$) and obesity ($p < 0.001$). Consumer concern

regarding breast cancer was the main barrier to clinicians prescribing MHT (56%). Only 50% of respondents agreed that it was easy to keep up with current recommendations regarding MHT. Preferred methods of obtaining current evidence regarding MHT were conferences (25%), followed by menopause society websites (21%) and journal articles (20%).

Discussion

This study is the first evaluation comparing knowledge and attitudes of endocrinologists, GPs and gynecologists concerning menopause and menopausal therapies post-WHI and the first to explore the menopause-related knowledge and attitudes of Australian HPs. The previous study comparing US gynecologists, primary-care providers and internists¹⁶ was conducted prior to completion of the estrogen-only WHI study²⁴. Our findings indicate that most HPs would prescribe MHT for symptomatic menopausal women, although variations exist between specialties in prescribing practices, including length of time for MHT. Only a minority of HPs would prescribe MHT for disease prevention in women 50–60 years with variation observed between specialties. A personal history of venous thrombosis and breast cancer was the main reason for not prescribing MHT. Results showed clinicians' knowledge gaps regarding non-hormonal therapies and bone/cardiovascular/metabolic health with no difference between GPs, endocrinologists and gynecologists.

A lack of awareness among HPs regarding menopause and MHT has been reported to be a major barrier to early detection and appropriate treatment²⁵. Indeed, clinicians' disagreement in menopause management indicates variation in the level of education and knowledge¹⁵. A recent online survey of 510 American obstetrics and gynecology residents demonstrated poor knowledge of menopause issues, indicating the need for development of an educational curriculum in menopause medicine²¹. Similarly, Wang and colleagues reported uncertainty concerning some possible risks and benefits of combined MHT among Chinese gynecologists, although knowledge regarding the effect of MHT on colon and endometrial cancer risk differed by specialties¹⁴. However, as described above, previous studies have involved

Table 2. Health professionals' self-reported knowledge and attitude regarding menopause and menopausal hormone therapy. Data are given as *n* (%). χ^2 analysis was used for comparison between specialty groups.

	Specialty				
Variable	General practitioners (n = 283)	Endocrinologists (n = 61)	Gynecologists (n = 401)	Total	p Value
HPs' self-reported knowledge					
Menopause physiology					0.43
knowledgeable	195 (74%)	38 (66%)	285 (73%)	518 (72%)	
limited knowledge & need to learn more	69 (26%)	20 (35%)	106 (27%)	195 (27%)	
Hormone therapy					0.36
knowledgeable	192 (73%)	38 (64%)	287 (73%)	517 (72%)	
limited knowledge & need to learn more	72 (27%)	21 (36%)	105 (27%)	198 (28%)	
Non-hormonal therapy					
knowledgeable	138 (53%)	26 (46%)	205 (53%)	369 (52%)	
limited knowledge & need to learn more	123 (47%)	31 (54%)	184 (47%)	338 (48%)	
Bone health					
knowledgeable	149 (56%)	38 (64%)	221 (57%)	408 (57%)	
limited knowledge & need to learn more	115 (44%)	21 (36%)	169 (43%)	305 (43%)	
Cardiovascular disease					0.93
knowledgeable	156 (59%)	34 (59%)	227 (58%)	417 (59%)	
limited knowledge & need to learn more	107 (41%)	24 (41%)	165 (42%)	296 (42%)	
Metabolic syndrome					0.14
knowledgeable	141 (54%)	26 (45%)	225 (58%)	392 (55%)	
limited knowledge & need to learn more	122 (46%)	32 (55%)	164 (42%)	318 (45%)	
HPs' self-reported attitude					
Prescribing MHT to symptomatic menopausal women					0.58
agree	242 (89%)	54 (92%)	348 (92%)	644 (91%)	
neutral	23 (9%)	4 (7%)	20 (5%)	47 (7%)	
disagree	7 (3%)	1 (2%)	11 (3%)	19 (3%)	
Prescribing MHT to non-symptomatic menopausal women					0.12
agree	92 (34%)	21 (36%)	117 (31%)	230 (32%)	
neutral	52 (19%)	18 (31%)	96 (25%)	166 (23%)	
disagree	129 (47%)	19 (33%)	170 (44%)	318 (45%)	
Treatment for hot flushes					0.07
MHT	186 (68%)	52 (90%)	295 (77%)	533 (75%)	
non-hormonal medication	23 (8%)	2 (3%)	24 (6%)	49 (7%)	
complementary & alternative therapy	6 (2%)	0	10 (3%)	16 (2%)	
compounded bioidentical hormone therapy	2 (1%)	0	4 (1%)	6 (1%)	
lifestyle modification	38 (14%)	3 (5%)	35 (9%)	76 (11%)	
others	18 (7%)	1 (2%)	15 (4%)	34 (5%)	
MHT for women with PM without contraindications					0.73
combined OCP	129 (47%)	31 (53%)	207 (54%)	367 (52%)	
oral MHT	85 (31%)	13 (22%)	97 (25%)	195 (27%)	
transdermal MHT	40 (15%)	12 (21%)	54 (14%)	106 (15%)	
hormone implant	3 (1%)	0	7 (2%)	10 (1%)	
compounded bioidentical hormone therapy	2 (1%)	0	2 (1%)	4 (1%)	
not to use MHT	0	0	0	0	
others	13 (5%)	2 (3%)	15 (4%)	30 (4%)	
MHT for women over 50 without contraindications					0.005
oral MHT	117 (43%)	14 (24%)	158 (41%)	289 (41%)	
transdermal MHT	146 (54%)	42 (73%)	185 (48%)	373 (52%)	
hormone implant	0	0	8 (2%)	9 (1%)	
compounded bioidentical hormone therapy	4 (2%)	0	5 (1%)	9 (1%)	
not to use MHT	0	1 (2%)	9 (2%)	11 (2%)	
others	4 (2%)	1 (2%)	18 (5%)	23 (3%)	
Duration of systemic MHT for women with PM					0.009
1–5 years	16 (6%)	1 (2%)	19 (5%)	36 (5%)	
6–10 years	52 (20%)	5 (9%)	46 (13%)	103 (16%)	
11–15 years	21 (8%)	3 (5%)	29 (8%)	53 (8%)	
until age 50–51 years	147 (58%)	40 (71%)	199 (57%)	386 (58%)	
indefinite	19 (8%)	7 (13%)	58 (17%)	84 (13%)	
Duration of systemic combined MHT for symptomatic women over 50 years					0.001
1–5 years	218 (86%)	48 (86%)	254 (72%)	520 (78%)	
6–10 years	25 (10%)	5 (9%)	49 (14%)	79 (12%)	
11–15 years	3 (1%)	1 (2%)	10 (3%)	14 (2%)	
>15 years	0	0	7 (2%)	7 (1%)	
indefinite	7 (3%)	2 (4%)	34 (10%)	43 (7%)	
Duration of systemic estrogen-only MHT for symptomatic women without uterus over 50 years					0.06
1–5 years	156 (61%)	32 (50%)	185 (52%)	373 (56%)	
6–10 years	57 (22%)	12 (22%)	71 (20%)	140 (21%)	
11–15 years	10 (4%)	1 (2%)	15 (4%)	26 (4%)	
>15 years	0	1 (2%)	10 (3%)	12 (2%)	
indefinite	31 (12%)	9 (16%)	73 (21%)	113 (17%)	

HPs, health professionals; GPs, general practitioners; PM, premature menopause (menopause <40 years); MHT, menopausal hormone therapy.

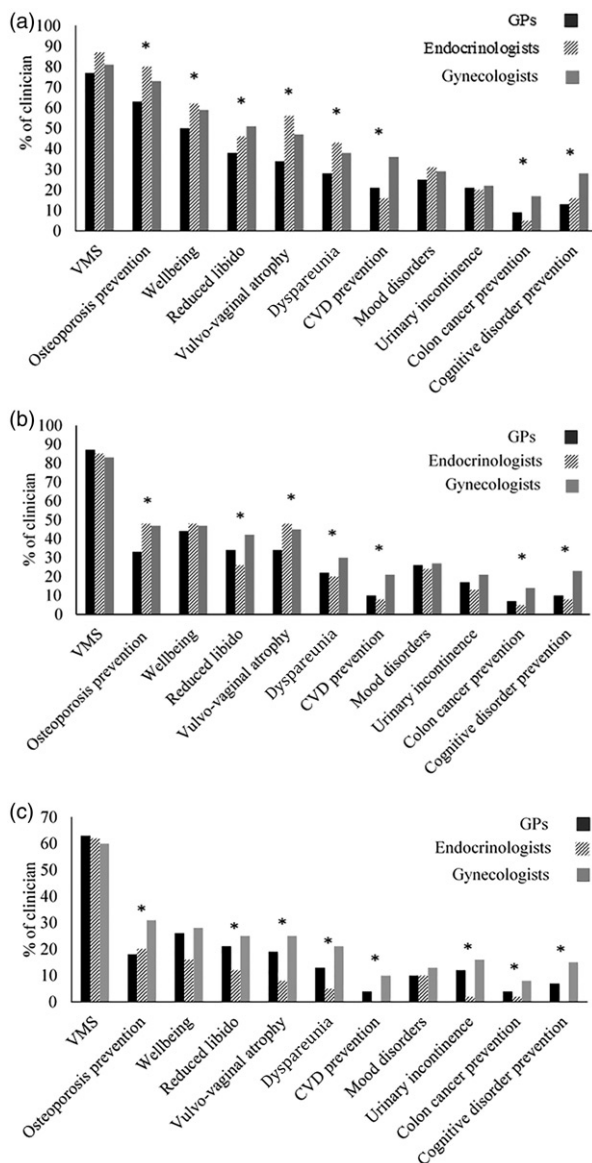


Figure 1. Reported indications for menopausal hormone therapy (MHT) prescribing according to specialty (GPs, endocrinologists or gynecologists) and age group of women including (a) premature menopause; (b) age 50–55 years; and (c) age 56–60 years. χ^2 analysis was used for comparison between specialty groups. Significant difference ($p < 0.05$) between specialty groups is indicated by * for each indication. VMS, vasomotor symptoms; CVD, cardiovascular disease.

gynecologists and there is limited information regarding differences between specialists involved in menopause management.

In the present study, younger HPs and new graduates report themselves to be knowledgeable regarding non-hormonal therapy. This may relate to the negative impacts of the WHI trial on MHT prescriptions and higher use of alternative products during recent years⁸. In a post-WHI study, new graduates were less certain regarding the benefits of MHT compared with experienced physicians²³. Prior to release of the results of the WHI study, MHT was routinely prescribed to menopausal women without contraindication, regardless of symptoms^{26–28}. However, over the recent two decades, systemic MHT is recommended more cautiously^{14,16}. Clinicians would predominantly recommend this therapy to symptomatic women.

Table 3. Membership of a menopause society and the likelihood of prescribing menopausal hormone therapy (MHT) for potential indications/contraindications of MHT. Odds ratio of menopause society members prescribing MHT for particular indications in women with premature menopause (< 40 years) or postmenopausal women aged 50–55 years (compared with non-members). A logistic regression analysis was used to measure the significant association between membership of menopause society and the odds of prescribing MHT.

Potential indications	Age (years)	Odds ratio (95% confidence interval)
Relief from vasomotor symptoms	<40	2.89 (1.64–5.09) ^a
	50–55	4.90 (2.23–10.76) ^a
Prevention of osteoporosis	<40	2.09 (1.36–3.22) ^a
	50–55	1.96 (1.36–2.77) ^a
Prevention of colon cancer	<40	1.23 (0.74–2.02)
	50–55	1.82 (1.09–3.03) ^a
Prevention of cognitive disorder	<40	1.53 (1.02–2.29) ^a
	50–55	1.39 (0.89–2.17)
Improve well-being	<40	1.76 (1.22–2.54) ^a
	50–55	2.36 (1.65–3.40) ^a
Manage vaginal bleeding	<40	0.82 (0.53–1.27)
	50–55	1.53 (0.99–2.38)
Prevention of cerebrovascular disease	<40	2.77 (1.92–4.00) ^a
	50–55	2.44 (1.60–3.75) ^a
Prevention of diabetes mellitus	<40	1.85 (0.90–3.80)
	50–55	0.95 (0.31–2.91)
Reduced libido	<40	1.82 (1.28–2.60) ^a
	50–55	2.08 (1.45–2.97) ^a
Atrophic vaginitis	<40	1.21 (0.85–1.72)
	50–55	1.39 (0.95–2.03)
Dyspareunia	<40	1.23 (0.85–1.77)
	50–55	1.76 (1.21–2.58) ^a
Urinary incontinence	<40	0.99 (0.65–1.53)
	50–55	1.12 (0.72–1.75)
Mood disorder	<40	2.36 (1.63–3.41) ^a
	50–55	2.52 (1.70–3.74) ^a

^a, $p < 0.05$.

In the current study, the combined oral contraceptive pill was reported as the first-line treatment for women with premature menopause, although evidence suggests less bone protection associated with this therapy²⁹. Transdermal MHT was the preferred treatment for women over 50 years. Endocrinologists seemed more likely to prescribe transdermal MHT for women at average age of menopause compared to other specialties, potentially, due to more awareness of the possible thromboembolic risks of oral MHT. Recent studies and guidelines have consistently demonstrated that transdermal MHT can be associated with a decreased risk of venous thrombosis compared to oral administration^{18,30,31}. In a large survey by Buhling and colleagues, 75% of German gynecologists reported a shift to transdermal MHT since publication of the WHI trial³².

Combined MHT would be advised by most clinicians for less than 5 years for women aged 50–60 years, whereas more gynecologists prefer to advise for a longer duration. Most HPs would also prefer estrogen-only therapy for 1–5 years for women without a uterus aged >50 years, although WHI evidence suggests no increased risk of cardiovascular disease or breast cancer with 7 years of treatment and 13 years of follow-up³³. This suggests a knowledge gap between the published literature and HP practice. As recommended in recent guidelines for management of women with premature ovarian insufficiency (POI)¹⁸, most HPs in our study would prescribe systemic MHT until 51 years for women with premature menopause, and variations by specialties were observed.

Table 4. Membership of a menopause society and the likelihood of prescribing menopausal hormone therapy (MHT) for potential indications/contraindications of MHT. Odds ratio of menopause society members prescribing MHT for particular contraindications in postmenopausal women (compared with non-members). A logistic regression analysis was used to measure the significant association between membership of menopause society and the odds of prescribing MHT.

Potential contraindications	Odds ratio (95% confidence interval)
Personal history of breast cancer	0.49 (0.24–1.00)
Family history of breast cancer	2.45 (1.54–3.90) ^a
Personal history of venous thromboembolism	1.51 (0.65–3.53)
Family history of venous thromboembolism	2.95 (1.84–4.72) ^a
Personal history of cerebrovascular disease	0.98 (0.54–1.78)
Personal history of ischemic heart disease	0.82 (0.47–1.43)
Hyperlipidemia	3.57 (2.08–6.14) ^a
Hypertension	5.83 (3.22–10.57) ^a
Personal history of uterine cancer	2.51 (1.54–4.09) ^a
Diabetes mellitus	2.59 (1.48–4.53) ^a
Obesity	2.41 (1.40–4.14) ^a
Patients' concern regarding breast cancer	3.12 (1.90–5.12) ^a

^a, $p < 0.05$.

Consistent with previous studies^{14,34}, our survey showed a general consensus between HPs in prescribing MHT for relief of vasomotor symptoms in women under 60 years. However, the variation between specialties in relation to MHT for disease prevention again suggests knowledge gaps and the potential variation in management between specialties. Similar to previous reports¹⁶, most HPs in our survey would not prescribe MHT for cardiovascular protection regardless of the woman's age. Recent POI guidelines¹⁸ recommend MHT 'to control future risk of CVD'. In a recent large survey assessing the prescribing practices of American GPs, gynecologists and wellness physicians for management of menopausal women, only small percentages of GPs/gynecologists advised hormone therapy (FDA-approved and compounded) for cardiovascular benefits compared to wellness physicians, although it was prescribed for longer term³⁴. Our study indicates that gynecologists and members of menopause societies were more likely to prescribe MHT for cardioprotection.

Although most HPs would prescribe MHT to women with premature menopause for osteoporosis prevention, only a minority would prescribe for osteoporosis prevention in women aged 50–60 years despite proven fracture prevention³³. This disparity may reflect both the difficulty in keeping up with current MHT guidelines/recommendations reported by 50% of respondents and the differences in recommendations between various government bodies, menopause/endocrine societies and medical colleges^{30,35–38}. Small percentages of clinicians would advise MHT for ameliorating incontinence and cognitive disorders at all ages. Systemic MHT may not be effective in prevention of urinary incontinence³⁰. However, the guideline of the European Society for Human Reproduction and Embryology recommends MHT at least until the average age of menopause for improving cognitive function in women with premature menopause¹⁸.

Despite recent reports indicating the protective effect of MHT against colorectal cancer³⁹, most clinicians in our survey were reluctant to prescribe combined estrogen and progesterone for this purpose. According to the recently published guideline of the International Menopause Society, MHT is not

recommended merely for prevention of colorectal cancer³⁰. Similarly, in the study by Wang and colleagues¹⁴, HPs were uncertain about this potential effect. However, more gynecologists in our survey tend to prescribe MHT to reduce colon cancer risk than GPs and endocrinologists.

Our study agrees with previous reports regarding potential contraindications to MHT prescribing, including a history of venous thrombosis, breast cancer, cerebrovascular disease, ischemic heart disease and uterine cancer^{14,16}. However, our study indicates variation between specialties and also with menopause society membership. GPs were less likely to prescribe MHT in women with a history of thromboembolic events than endocrinologists and gynecologists. Endocrinologists seem to differ from GPs and gynecologists in recommending MHT in the cases of hyperlipidemia, hypertension, diabetes and obesity, which may reflect greater knowledge of these areas. Interestingly, members of a menopause society were more likely to prescribe MHT in the setting of potential indications and contraindications, which may indicate a better understanding and perspective of their knowledge of MHT.

Although knowledge gaps may influence HPs' attitudes and prescribing practices, consumer knowledge and preferences are also important. Consistent with a previous study¹⁶, approximately 50% of HPs were unlikely to prescribe MHT to women who have concerns about breast cancer. Indeed, patients' concerns regarding breast cancer and other potential MHT risks and consumer preferences for alternative therapies were considered the main barriers to prescribing MHT. A previous study indicating the disparity between gynecologists/partners self-use of MHT and prescribing for the general population shows the positive attitude of clinicians to MHT versus women's concerns regarding MHT^{22,40,41}. This may relate to the effect of the media following the WHI study³².

There were several potential limitations to this study. Since the questionnaires were available online, we could not precisely specify the response rate of HPs and only a small percentage of endocrinologists returned the survey compared to GPs/gynecologists. Self-reported knowledge and attitude were other limitations of this survey. However, the key strengths of this study were (1) the novelty of research assessing Australian HPs from various specialties in the post-WHI era; (2) the large sample size, and (3) HPs' mean work experience of 20 ± 11.14 years.

Conclusion

Although most HPs will recommend MHT for symptomatic menopausal women, variations exist between specialties in prescribing practices. HPs' knowledge gaps, relating to non-hormonal therapies, bone health, cardiovascular disease and metabolic syndrome, and also perceived consumer concerns regarding breast cancer risk are barriers to prescribing MHT. As such, targeted HP and consumer education addressing particular menopause-related topics and age groups is needed. Collaboration between menopause societies, government, medical colleges and consumer groups is needed to facilitate the provision and dissemination of evidence-based

consistent information/messages regarding menopause and menopausal therapies.

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Conflict of interest Dr Amanda Vincent is a member of the Editorial Board of *Climacteric* and President-Elect of the Australasian Menopause Society. This study was presented as an oral presentation at the Australasian Menopause Society Congress, Fremantle, Western Australia, 2016. There are no other conflicts of interest.

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Chapter 3: Evidence Synthesis

3.1. Introduction

Gynaecological cancers (GC), including endometrial and ovarian cancer, represented 9.7% of all new female cancer cases diagnosed in Australia in 2019 (85). Women with GC have a 5-year relative survival rate of 69% (85) and survivorship issues are of increasing importance. Approximately 30% of GC survivors are premenopausal at diagnosis and will develop EM/POI due to cancer treatment including bilateral oophorectomy (BSO) (85, 86). BSO is associated with multiple health risks including osteoporosis, CVD and early mortality (29, 42, 44). Although MHT is beneficial in reducing the risks of osteoporosis, CVD and mortality, it is generally contraindicated in the setting of oestrogen sensitive cancer such as breast or endometrial cancer (6). Therefore, alternatives to hormone therapy such as lifestyle modifications may be beneficial where MHT is contraindicated or in addition to MHT (6). Systematic reviews of lifestyle modifications in breast cancer survivors have indicated that physical activity and exercise is associated with a decreased risk of breast cancer-specific and overall-mortality and an improved QoL (87, 88). Also, the potential benefits of lifestyle modifications (including a healthy diet and exercise) on cardiovascular and bone health, physical and emotional wellbeing and reducing the non-cancer mortality in menopausal women has been previously demonstrated (89, 90). However, evidence regarding the beneficial effects of lifestyle interventions in GC survivors is limited. Therefore, the first study in this chapter explores the effect of lifestyle interventions on cancer recurrence, cancer free survival and QoL in endometrial and cancer survivors.

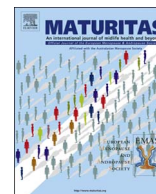
HPs' knowledge gaps regarding menopause management and variations in prescribing practices (4, 57) have raised the need for evidence-based recommendations in clinical practice. The US Institute of Medicine define CPGs as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (91). CPGs have the potential to decrease variations in the clinical practice, enhance translation of research into practice, and improve healthcare quality (92). However, significant limitations and variations exist in the methodological quality and content of the CPGs (93-95). Numerous CPGs exist in menopause management which are intended to improve patient outcomes and promote cost-effective clinical care. However, their content and methodological quality are unknown and has not been previously assessed. The second study in this chapter provides the results of the quality and content appraisal of the CPGs of menopause management and also a summary of the EM/POI recommendations from high scored CPGs which informed the development an EM/POI management algorithm.

3.2. Effects of lifestyle modification on cancer recurrence, overall survival and quality of life in gynaecological cancer survivors: A systematic review and meta-analysis.

Summary

This systematic review aimed to determine whether lifestyle interventions can prevent cancer recurrence and improve overall survival and QoL in endometrial and ovarian cancer survivors. Electronic databases were searched to identify the relevant published literature. We included RCTs in which a lifestyle intervention were compared with a control group in GC survivors. Systematic search indicated that there were no papers specific to EM and only 3 studies were identified overall. No effect of lifestyle modification was demonstrated in the two studies included in the meta-analysis. However, the paucity of studies limits the conclusions that can be drawn and highlights the need for further research.

Yeganeh L, Harrison C, Vincent AJ, Teede H, Boyle JA. Effects of lifestyle modification on cancer recurrence, overall survival and quality of life in gynaecological cancer survivors: A systematic review and meta-analysis. *Maturitas* 2018, 111: 82-9.



Effects of lifestyle modification on cancer recurrence, overall survival and quality of life in gynaecological cancer survivors: A systematic review and meta-analysis



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ABSTRACT

The benefits of lifestyle interventions for women who have survived gynaecological cancer (GC) remain unclear. This systematic review aimed to determine the effect of lifestyle interventions on cancer recurrence, overall survival and quality of life (QoL) in women with GC. We searched Medline, Embase, PsycINFO and EBM Reviews from June to July 2016 to identify relevant literature. We included randomized controlled trials in which a lifestyle intervention (diet, weight loss, physical activity and/or behavioural interventions) were compared with a control condition (usual care, placebo or other lifestyle interventions) in women who had survived endometrial or ovarian cancer. Primary outcomes included cancer recurrence and overall survival and the secondary outcome was QoL. Data extraction and risk-of-bias assessment were performed by two independent reviewers. A random-effects meta-analysis model was used to calculate mean differences (md) and 95% confidence intervals (CI). The literature search yielded 928 citations and three trials met the inclusion criteria. No randomized controlled trial assessed the effect of lifestyle interventions on cancer recurrence or survival. Meta-analysis of two randomized controlled trials on the effect of lifestyle interventions on total QoL at 3 or 6 months post-intervention showed no significant difference between intervention and control groups [(md; 1.60; 95% CI, −1.65 to 4.85) and (md; 2.07; 95% CI, −1.80 to 5.94), respectively]. That is, lifestyle intervention had no effect on overall QoL or individual QoL domains (physical, emotional, social wellbeing and fatigue) in GC survivors.

Systematic review registration: PROSPERO CRD42016043719.

1. Introduction

Gynaecological cancers (GCs) are amongst the most common malignancies affecting women with an estimated 61,000 and 22,000 new cases for endometrial and ovarian cancers in 2017, respectively [1]. Uterine cancer has a 5-year relative survival rate of 78%–83% in Australia, USA and UK [1–3]. However, despite significant improvements in survival rates over time, many ovarian cancers are still diagnosed at an advanced stage contributing to poor prognosis with overall 5-year survival rate of 44%–50% [1,4,5]. Therefore, research to identify factors that can improve survival after diagnosis of GC would be of great value.

The role of a healthy lifestyle on prevention of GC has been established over the past several decades [6,7]. In recent years, studies have focused on the impact of healthy behaviours on cancer survivorship. High body mass index (BMI) is associated with an adverse GC prognosis [8,9] and maintaining a healthy weight range via lifestyle modifications including diet and exercise could potentially reduce the risk of recurrence. Observational studies suggest that pre-diagnosis, healthy diet (fruits/vegetables based or a low fat diet) and regular physical activity may improve survival rates among ovarian cancer survivors [10–12]. However, a study by von Gruenigen et al. observed that most endometrial cancer survivors followed a poor and unhealthy lifestyle, as only 1% of participants adhered to all three American Cancer Society

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Guidelines on nutrition and physical activity and the majority had abdominal obesity [13]. Although the underlying mechanism by which a healthy lifestyle can modify endometrial and ovarian cancer risk or prognosis remains unclear, it is postulated that modulation of estrogen metabolism, inflammation biomarkers and oxidative DNA damage could play a role [14–16].

Approximately 25% of women diagnosed with GC are under 50 years of age and will develop menopause due to bilateral oophorectomy (BO) as part of their cancer treatment [17], which leads to significant morbidity and impaired quality of life (QoL) [18]. Early menopause (before 45 years), secondary to BO for benign conditions is associated with premature death including increased cardiovascular mortality [19]. Lifestyle factors including diet and exercise can reduce cardiovascular disease risk and non-cancer mortality in premenopausal and postmenopausal women [20,21].

Gynaecological cancers, particularly recurrent disease, are associated with emotional, psychological, physical and social challenges [22]. The positive role of diet, exercise and behavioural interventions on physical function, weight and overall QoL in women with GC has been previously demonstrated [23,24]. In a quasi-experimental study on ovarian cancer survivors, physical, emotional, social and functional wellbeing were significantly improved following an intensive health care intervention including group education, self-help support and 8 weeks home-based exercise/relaxation therapy (3 times/week) [25].

This systematic review aimed to determine whether lifestyle interventions can prevent cancer recurrence and improve overall survival and QoL in endometrial and ovarian cancer survivors.

2. Methods

2.1. Search strategy

This review adheres to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The systematic search was based on the selection criteria and combining MeSH terms and text words using the OVID platform. Electronic databases including Medline, Embase, PsycINFO and all EBM Reviews incorporating Cochrane Database of Systematic Reviews were searched to identify the relevant published literature. We also searched the bibliographies of the retrieved studies to identify any additional papers. The search strategy was limited to English language articles and there was no restrictions on date of publication. The keywords for searches are detailed in [Appendix A](#). The review protocol is according to PRISMA statement and is available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043719.

2.2. Criteria for study inclusion

2.2.1. Types of studies

We included randomized controlled trials and randomized parallel group trials including pilot studies.

2.2.2. Participants

Endometrial and ovarian cancer survivors aged over 18 years with no evidence of recurrence were included.

2.2.3. Interventions

Studies with a lifestyle intervention including those comprising dietary modification, nutritional supplementation, and/or increased physical activity with or without behavioural interventions such as cognitive therapy, relaxation therapy, meditation and psychotherapy were considered for inclusion in this review. There were no restrictions on frequency, duration and intensity of interventions. There was also no limitation on intervention setting (e.g. hospital based, home based, individual/group counselling, face to face, telephone or computer based counselling).

2.2.4. Controls

We included studies comparing lifestyle intervention to usual care, placebo or any other lifestyle intervention.

2.2.5. Outcome measures

The primary outcomes of interest were cancer recurrence and overall survival. The secondary outcome was QoL.

2.3. Data collection

A preliminary screening was performed through titles and abstracts of all articles retrieved by the first reviewer (LY). Duplicate articles and those not meeting the inclusion criteria were excluded from further review.

2.4. Data extraction and risk of bias assessment

Two reviewers (LY and CH) independently extracted data and assessed risk of bias. Any disagreement was resolved by discussion to reach a consensus. Data was extracted from included studies according to the selection criteria. Information was collected on general characteristics of the trials (authors, year of publication, country of origin and study design), intervention (duration, intervention components and setting), participants (age, selection criteria, sample size, randomized and analysed, withdrawals/losses to follow-up) and results (mean and standard deviation for continuous variables, within and between group p-values). Where required, the corresponding author was contacted for additional data.

Articles were also assessed for risk of bias using a standard template for critical appraisal of a randomized controlled trial [26]. Quality appraisal components consisted of specified selection criteria, method of randomization, allocation concealment, blindness of patients/investigators/health care providers, outcome assessment, statistical analysis, controlling the confounders, study power and authors conflict of interest. The articles were assessed as high, low, or unclear risk using recommendations for judging risk of bias of the “Cochrane Handbook for Systematic Reviews of Interventions” [27].

2.5. Data synthesis

Review Manager Software (RevMan 5.3-2014) was used for the meta-analysis. The homogeneity of studies tested with an I^2 (> 50% indicating heterogeneity). A random-effects model was used for the meta-analysis, using mean difference/95% CI.

3. Results

3.1. Results of the search

A detailed diagram of the review process is shown in [Fig. 1](#). The initial literature search was conducted from June to July 2016, yielded 928 citations. We repeated the search strategy in July 2017 to update the review prior to publication and no further articles were identified. Following the screening of titles and abstracts, 16 potentially eligible studies were identified for full text review and finally three studies met the inclusion criteria and were included for review.

925 out of 928 studies were excluded for the following reasons: duplicate references, non-randomised controlled trial, single arm studies, no lifestyle intervention, participants did not meet our criteria, women diagnosed with other types of cancers and studies focus on primary cancer prevention or risk reduction.

3.2. Included studies

Of the 928 studies included for review, no study was found to evaluate the effect of lifestyle modification on cancer recurrence and

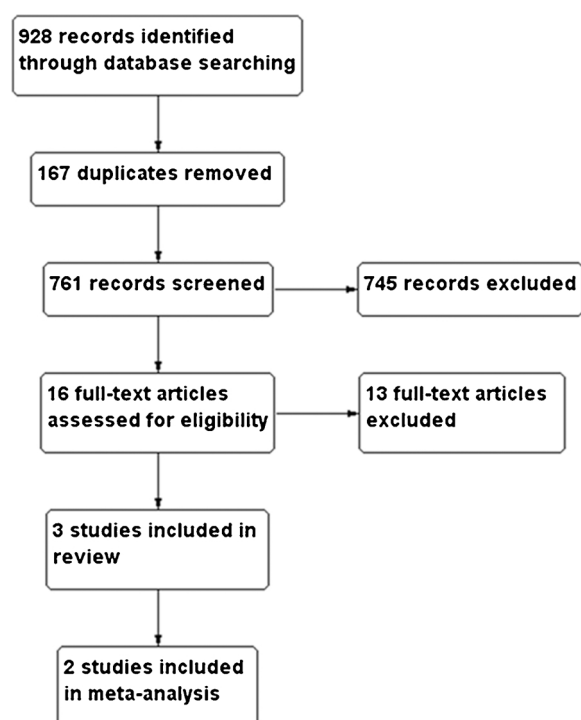


Fig. 1. PRISMA flow diagram of selection of studies.

overall survival. However, three trials [23,28,29] evaluated the secondary outcome: QoL (Table 1).

A total of 172 GC survivors/participants (52 ovarian/120 endometrial cancer) were involved ranging in age from 53 to 55 years.

3.3. Outcomes

QoL was documented in three trials published between 2009 and 2014. Data related to the various QoL domains including physical, emotional, social, and functional well-being and fatigue and depression were reported (Table 1).

In the RCT reported by McCarroll et al. [23], a lifestyle intervention comprising a healthy nutrition, exercise and cognitive behavioural modifications over six months successfully reduced body mass index and increased self-efficacy in overweight/obese endometrial cancer survivors. QoL domains of fatigue and physical function were also significantly improved at three months ($p = 0.008$) and six months (0.048), respectively, in the intervention group compared with those who received the usual care. There was also a significant within group improvement in overall QoL, over the 6 month intervention (baseline, 79.8 ± 13.4 versus three months, 87.1 ± 7.6 , $p = 0.008$), (baseline, 79.8 ± 13.4 versus six months, 86.6 ± 9.3 , $p = 0.0005$). Conversely, von Gruenigen et al. [28] reported that a lifestyle intervention focusing on diet, exercise and cognitive behaviour counselling was not associated with a significant change in QoL or depression in a similar patient population. However, self-efficacy was significantly improved in women who had weight loss versus those who gained weight [28]. Finally, no significant group difference was found in the third trial reporting the effect of dietary interventions including a low-fat/high fibre diet (LFHF) or a diet containing fruit and vegetable juice concentrates (FVJC) and soy beverages on certain aspects of health related QoL in ovarian cancer survivors. However, total carotenoids, α -carotene and β -carotene levels were significantly increased in both groups after 6 months intervention [29].

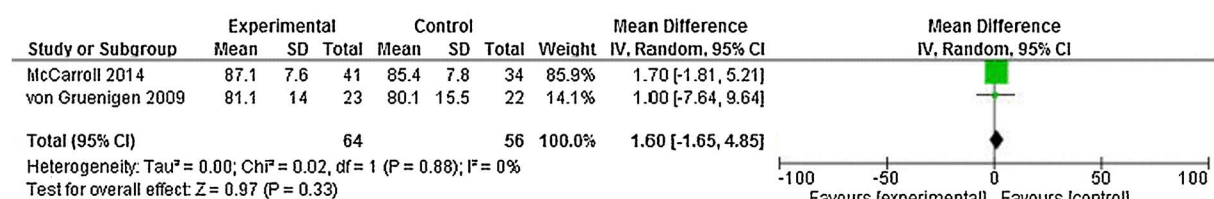
Meta-analysis of two RCTs [23,28] assessing the effect of diet, exercise and cognitive behavioural interventions on QoL at 3 and 6 months post-intervention showed no significant difference between the

Table 1
Summary of included studies on the effect of lifestyle intervention on quality of life in women with Gynaecological cancer.

Author/year/country	Sample size	Aims	Study design	Outcome measures	Lifestyle intervention	Comparison
McCarroll et al, 2014, USA [23]	75	To evaluate the effect of a lifestyle intervention on self-efficacy, QoL and weight loss in overweight/obese stage I–II endometrial cancer survivors	RCT	<ul style="list-style-type: none"> BMI QOL (FACT-G) Self-efficacy (WEL) 	Six months lifestyle interventions including nutrition, exercise and behavioural modification, on a group and individual basis	Usual care (informational brochure addressing better health/weight control)
von Gruenigen et al, 2009, USA [28]	45	To assess the effect of lifestyle interventions on QoL, depression, self-efficacy and eating behaviour changes in overweight and obese stage I–II endometrial cancer survivors	RCT	<ul style="list-style-type: none"> Anthropometric data QOL (FACT-G) self-efficacy (WEL) Depression (BDI) Eating behaviour (TFEQ) Functional status (SF-36) 	Six months exercise/nutritional/cognitive-behavioural counselling	Usual care (informational brochure addressing the benefits of exercise/healthy nutrition)
Paxton, et al, 2012, USA [29]	52	To assess the feasibility and effect of two dietary interventions in stage II–IV ovarian cancer survivors	Randomized parallel group	<ul style="list-style-type: none"> Serum carotenoid and tocopherol levels Dietary intake Anthropometry Health-related QoL at baseline/6 months (SF-36) 	<p>LFHF group had 5 serves vegetables/day; 16 ounces vegetable juice/day; 3 serves fruit/day; 30 g fiber/day; and $\leq 20\%$ energy from fat</p> <p>FVJC group had a modified National Cancer Institute diet, “5 A Day” program (i.e., ≥ 5 serves fruits and vegetables/day and ≥ 25 g fibre/day) with reduced fat, 4 FVJC capsules/day; and 33 g soy-based beverage powder/day, which includes 5 g fibre</p>	-

Note: FACT-G; Functional Assessment of Cancer Therapy-General, WEL; Weight Efficacy Lifestyle, BDI; Beck Depression Inventory, TFEQ; Three Factor Eating Questionnaire, SF-36; Short Form-36, LFHF; low fat high fibre, FVJC; fruit and vegetable juice concentrates.

a. Global quality of life at 3 months



b. Global quality of life at 6 months

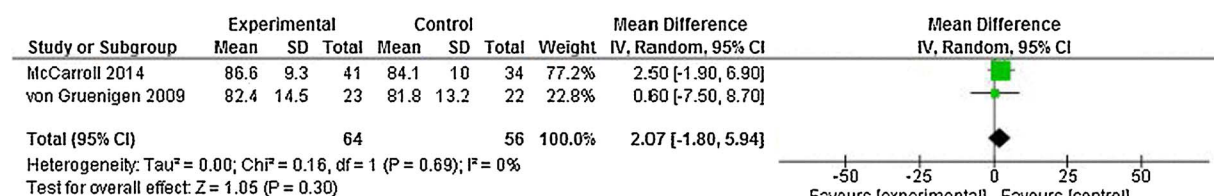
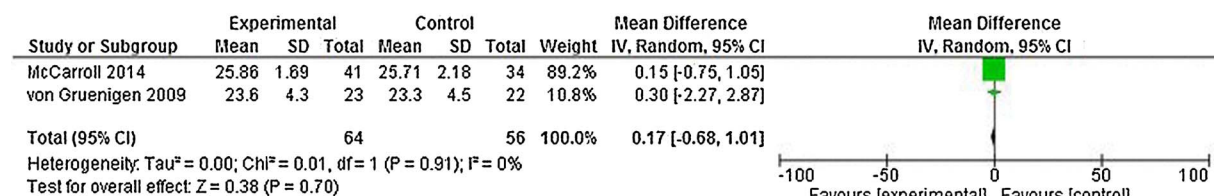
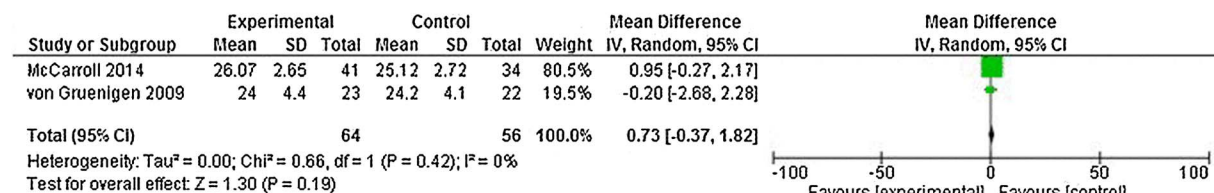


Fig. 2. Global quality of life.

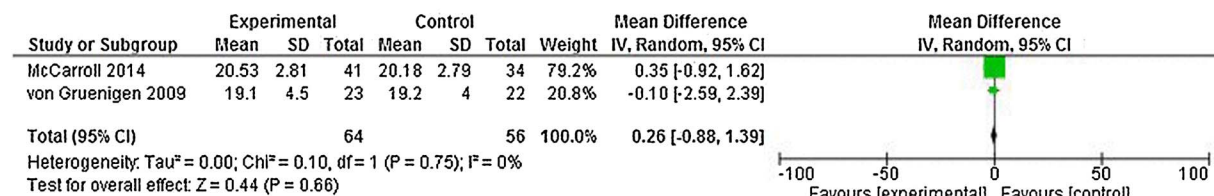
a. Physical wellbeing at 3 months



b. Physical wellbeing at 6 months



c. Emotional wellbeing at 3 months



d. Emotional wellbeing at 6 months

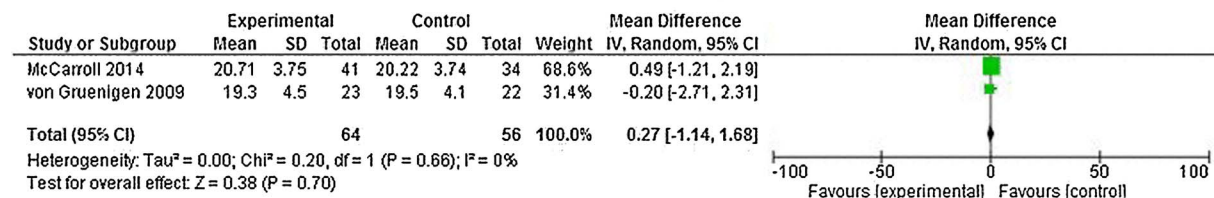


Fig. 3. Quality of life domains: Physical wellbeing and Emotional wellbeing.

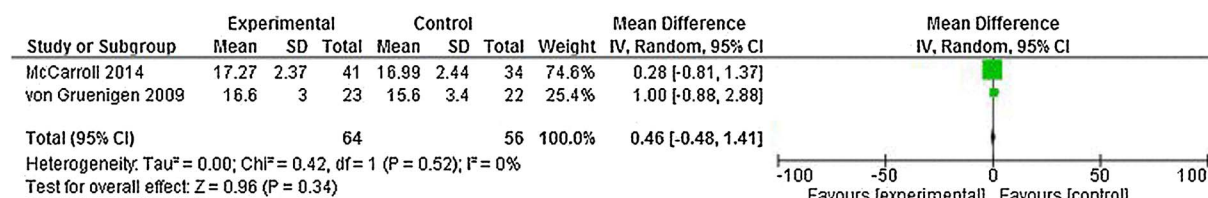
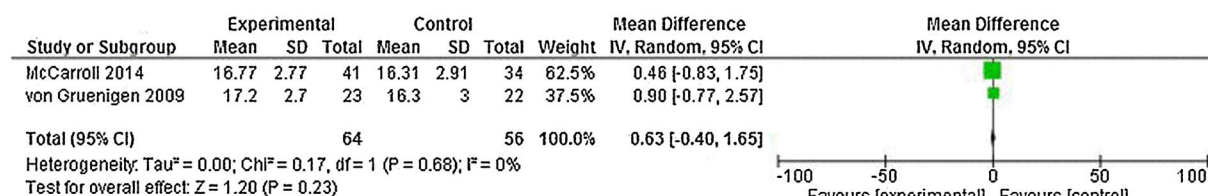
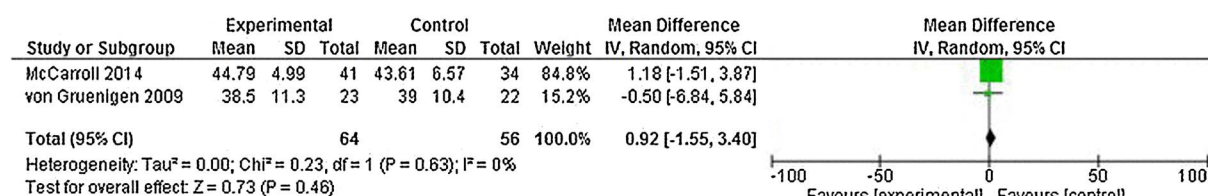
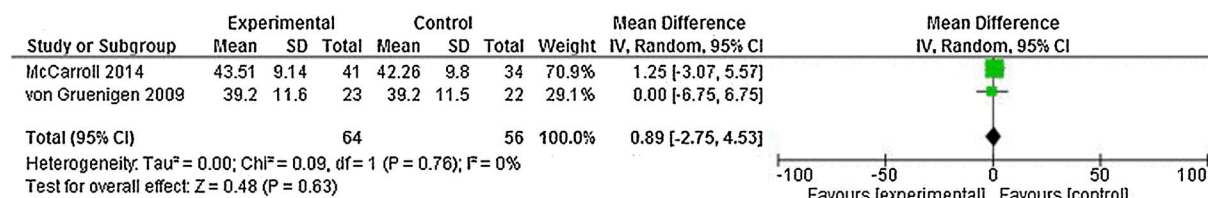
a. Social wellbeing at 3 months**b. Social wellbeing at 6 months****c. Fatigue at 3 months****d. Fatigue at 6 months**

Fig. 4. Quality of life domains: Social wellbeing and Fatigue.

intervention and control groups [(the mean diff; 1.60; 95% CI, -1.65 to 4.85, $p = 0.33$) and (the mean diff; 2.07; 95% CI, -1.80 to 5.94, $p = 0.30$) respectively; Fig. 2]. Additionally, there was no significant difference between intervention and control groups in terms of physical/psychological/social/fatigue domains of QoL after 3 and 6 months intervention (Fig. 3 and Fig. 4).

3.4. Risk of bias in included studies

We assessed the overall risk of bias in all trials as high. All trials were at a high risk for selection bias, as they did not provide sufficient information to confirm the adequacy of allocation concealment. Studies were also at risk of detection bias due to non-blinding of outcome assessment. Also the method of randomization and mode of allocation were not sufficiently described across studies. Blinding was reported in one study with health care providers blinded to the intervention [29].

4. Discussion

This systematic review found no data to inform whether lifestyle intervention can prevent cancer recurrence or improve overall survival in women with GC. There was also no benefit shown on lifestyle intervention on improvement in QoL.

A limited number of observational studies have demonstrated a statistically significant association between diet and exercise and GC

prognosis [10,11]. Higher pre-diagnosis diet quality is associated with reduced mortality in ovarian cancer survivors after adjusting for potential confounders [12]. Similarly, in a large prospective cohort study of Australian women diagnosed with epithelial ovarian cancer, high consumption of vegetables and foods rich in vitamin E was significantly correlated with a lower rate of cancer-related mortality [11].

Estrogen metabolites have been shown to have a role in breast and gynaecological malignancies [30]. Diets containing Indole-3 Carbinol such as yellow and Cruciferous vegetables can alter the level of estrogen metabolites and suppress ovarian cell proliferation [31,32]. Mounting evidence suggests a role of inflammatory markers such as C-reactive protein and interleukins in ovarian cancer incidence [33]. Therefore, an anti-inflammatory diet including isoflavones, vitamin E, β -carotene, fibre and unsaturated fatty acids, as measured by the “dietary inflammatory index” may be associated with reducing the risk of ovarian cancer [34], yet we found no clinical trial in GC survivors and further research is required.

Considering the potential association of BMI and GC prognosis [9], adequate physical activity and a healthy diet may play a significant role in weight management and reduced risk of mortality. Animal model studies have demonstrated an inhibitory effect of calorie restriction on tumour growth that is potentially correlated with steroid hormone metabolism, reduced insulin-like growth factor-1 and gene expression changes [35,36].

In a large prospective study, rigorous physical activity prior to

ovarian cancer diagnosis was associated with reduced risk of cancer and non-cancer related mortality [10]. Exercise may improve antioxidant capacity in cancer patients and protect against “oxidative DNA damage” as a potential cause of cancer [15]. However, we found no randomised controlled trials (RCTs) assessing exercise interventions on GC prognosis and research in this area is warranted.

Premenopausal women with GC develop early menopause following cancer treatment which may be associated with higher CVD risk, osteoporosis and all-cause mortality compared to women with natural menopause, as demonstrated in observational studies of women with BO for benign conditions [37,38]. The Women's Health Initiative observational study of menopausal women reported that adherence to a high quality diet reduced the risk of chronic disease mortality, including cardiovascular and cancer related mortality [39]. Lifestyle modifications including weight loss, healthy nutrition (high consumption of fruits/vegetables/grains, fish twice/week and a low fat diet) and regular physical activity (at least 150 min/week of moderate intensity physical activity) are recommended by recent menopause guidelines to prevent menopause-related morbidity and mortality [40,41]. We found no studies reporting on cardiovascular risk factors in GC survivors and we are left to rely on the extensive body of literature in the general population showing improvement of these risk factors with lifestyle intervention [42].

Medically or surgically induced early menopause adversely impacts on QoL [43] and while menopausal hormone therapy (MHT) significantly improves QoL in symptomatic menopausal women [44], this therapy is contraindicated in some women with GC and additional therapeutic options such as lifestyle intervention may be beneficial.

The current meta-analysis was based on two RCTs in women with endometrial cancer [23,28] with no improvement noted in global QoL or individual domains including physical/emotional/social wellbeing and fatigue following lifestyle intervention. This non-significant overall effect may relate to the low number of studies (n = 2) included in the meta-analysis, small sample sizes and high-risk of bias across studies. Additionally, the trials included in this meta-analysis did not provide information regarding the use of MHT by participants. MHT can be used by women with grade I endometrial cancer and some types of ovarian cancer [45,46] and has positive effects on QoL which could potentially mask/confound the effects of a lifestyle intervention. Only one diet-based interventional trial [29] assessed QoL in ovarian cancer survivors and no improvement in certain components of health related QoL was observed in those receiving either a low fat, high fibre diet or a diet containing fruit and vegetable juice over six months, using the 36-item short form (SF-36) health survey. This study was not included in the meta-analysis due to varying study population, lifestyle intervention and QoL scoring [29].

Previous single-arm and non-randomized trials of GC survivors evaluating QoL following home-based exercise/nutritional interventions, have reported inconsistent results [25,47,48]. In a recent wait-list controlled trial on obese endometrial cancer survivors, a three month group/individual-based physical activities significantly improved QoL [49]. In a pilot study, moderate increase in health related QoL was found following 12 weeks cognitive behavioural interventions in women with epithelial ovarian cancer [50].

4.1. Study limitations

The limited number of eligible RCTs included in this review, limit interpretation of the effect of lifestyle modification on cancer recurrence, survival and QoL with future high-quality research required. Included studies were heterogeneous, contained small sample sizes and were deemed to be at high risk of bias, further impacting interpretation of results.

4.2. Conclusion

In conclusion, this systematic review and meta-analysis emphasises the limited available high-quality evidence regarding the effect of lifestyle modification on cancer recurrence, survivorship and QoL in GC survivors. Our results found no beneficial effect of lifestyle interventions on global QoL or physical/emotional/social wellbeing and fatigue domains among women with GC. Future research would benefit from well-designed trials with large sample sizes, longer interventions and follow-up to assess the role of lifestyle interventions on cancer recurrence, disease free survival and QoL in women with GC.

Contributors

Ladan Yeganeh designed the study, screened search results, extracted and analysed data and drafted the manuscript.

Cheryce Harrison contributed to data extraction and reviewed the manuscript.

Amanda J Vincent contributed to study design and manuscript preparation, and provided clinical expertise and supervision.

Helena Teede provided clinical expertise and supervision and reviewed the manuscript.

Jacqueline A Boyle contributed to study design and manuscript preparation, and provided clinical expertise and supervision.

Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

This article has undergone peer review.

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Appendix A. Search strategy

1. Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or neoplasm* or malignan* or tumor* or tumour* or carcinom*)).mp.
3. Endometrial Neoplasms/
4. (endom* adj5 (cancer* or neoplas* or carcinom* or adeno-carcinom* or malignan* or tumor*or tumour*)).mp.
5. ((uter* and lining) adj5 (cancer* or tumor* or tumour* or neo-plas* or malignan* or carcinoma* or adenocarcinoma*)).mp.
6. 1 or 2 or 3 or 4 or 5
7. diet\$.mp
8. nutrition\$.mp
9. meal\$.mp
10. food\$.mp.
11. (Energy adj3 restrict\$).mp.
12. (Energy adj3 reduc\$).mp.
13. kilojoule\$.mp.
14. calor\$.mp.
15. hypocaloric.mp.
16. Feeding behaviour\$.mp.
17. Feeding behavior\$.mp.
18. eating behaviour\$.mp.
19. eating behavior\$.mp.

20. exp diet/
 21. exp diet therapy/
 22. exp nutrition therapy/
 23. exp food/
 24. exp feeding behavior/
 25. (diet\$ or diet\$ therap\$ or diet\$ modification\$ or diet\$ interven-
 tion\$ or diet\$ counsel\$).mp.
 26. exp Food Habits/
 27. isocaloric.tw.
 28. Energy Intake/
 29. or/7-28
 30. exercise\$.mp.
 31. exercise therapy.mp.
 32. exertion.mp.
 33. physical fitness.mp.
 34. physical activit\$.mp.
 35. physical performance.mp.
 36. sport\$.mp.
 37. (strength adj2 training).mp.
 38. resistance training.mp.
 39. (aerobic\$ adj2 training).mp.
 40. (endurance adj2 training).mp.
 41. physical training.mp.
 42. (strength\$ adj2 exercise\$.mp.
 43. (weight-bearing adj2 exercise\$.mp.
 44. (Resistance adj2 exercise\$.mp.
 45. (Aerobic\$ adj2 exercise\$.mp.
 46. (Endurance adj2 exercise\$.mp.
 47. (Physical adj2 exercise\$.mp.
 48. exp exercise/
 49. exp exercise therapy/
 50. physical exertion/
 51. exp sports/
 52. exp physical endurance/
 53. exp Yoga/
 54. exp sports/or exp bicycling/or exp running/or exp swimming/or
 exp walking/
 55. exp Physical Fitness/
 56. or/30-55
 57. exp cognitive therapy/
 58. exp Psychophysiology/
 59. exp relaxation techniques/
 60. exp relaxation technique/
 61. exp Relaxation Therapy/
 62. (cognitive adj2 therap\$.mp.
 63. (relax\$ adj2 technique\$.mp.
 64. relax\$.mp.
 65. exp Meditation/
 66. kinesiotherap\$.mp.
 67. exp Psychotherapy/
 68. Psychotherap\$.mp.
 69. exp Behavior Therapy/
 70. (Behavio\$ adj2 therap\$.mp.
 71. risk reduction behavior/
 72. (risk reduction adj2 behavio\$.mp.
 73. behavior control/
 74. (behavio\$ adj2 control).mp.
 75. exp Behavior/
 76. behavio?r.mp.
 77. exp health behavior/
 78. (health adj2 behavio\$.mp.
 79. behavio?r\$ coping strateg\$.mp.
 80. or/57-79
 81. exp life style/
 82. exp life change events/
 83. (life*style adj2 change\$.mp.

84. (life*style adj2 intervention\$.mp.
 85. (life*style adj2 modif\$.mp.
 86. (life*style adj2 choice\$.mp.
 87. (life?style or life style).mp.
 88. life?style program.mp.
 89. or/81-88
 90. ((weight or BMI or body mass index) and (preser\$ or maintain\$ or
 management or maintenance or reduc\$ or los\$ or decreas\$ or
 control)).tw.
 91. (((weight adj3 lo\$) or weight) adj3 reduc\$.tw.
 92. (((body mass index adj2 los\$) or BMI) adj2 los\$.tw.
 93. (((body mass index adj2 reduc\$) or BMI) adj2 reduc\$.tw.
 94. (((body mass index adj2 decreas\$) or BMI) adj2 decreas\$.tw.
 95. body weight changes/or weight gain/or weight loss/
 96. or/90-95
 97. 29 or 56 or 80 or 89
 98. 96 or 97 (weight loss OR all types of lifestyle)
 99. 96 and 97 (weight loss AND all types of lifestyle)
 100. 6 and 98 (weight loss OR all types of lifestyle AND cancer)
 101. 6 and 99 (weight loss AND all types of lifestyle AND cancer)

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3.3. Menopause Guideline appraisal and algorithm development for Premature Ovarian Insufficiency

Summary

We aimed to systematically evaluate the quality of menopause CPGs, identify menopause topics included in the CPGs, summarize EM/POI recommendations provided by high scored CPGs and develop EM/POI management algorithms. Our systematic search and AGREE II appraisal of CPGs indicates variability in quality domains between guidelines. Analysis of CPG content and recommendations revealed significant deficiencies, variability and lack of high-quality evidence to guide management. CPGs have evidence limitations and recommendation gaps indicating the need for further research.

Yeganeh L, Boyle JA, Wood A, Teede H, Vincent AJ. Menopause Guideline appraisal and algorithm development for Premature Ovarian Insufficiency. Submitted to Maturitas.

Title page

Menopause Guideline appraisal and algorithm development for Premature Ovarian Insufficiency

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Objectives: Clinical practice guidelines (CPGs) are systematically developed statements that guide clinicians to provide appropriate healthcare. This study aimed to: 1) systematically evaluate the quality of menopause management CPGs; 2) to identify menopause topics included in the CPGs; 3) to summarize early menopause (EM) or premature ovarian insufficiency (POI) recommendations provided by high scored CPGs; and 4) to develop EM/POI management algorithms.

Study design: A systematic search for CPGs published between 2012-2017 was conducted using Medline, Embase, All EBM, CPG databases and medical websites. Appraisal was conducted by 4 independent reviewers using the Appraisal of Guidelines for Research & Evaluation II instrument (AGREE II). Inter-rater reliability was calculated using the Intraclass Correlation Coefficient. Recommendations regarding EM/POI were extracted from high scored CPGs and translated into a management algorithm with refinement using expert clinician feedback.

Results: Systematic search yielded 22 CPGs for review. Only 2 CPGs were assessed as high quality, with 10 average and 10 considered low quality. Scope and purpose ($73\% \pm 15\%$) and clarity of presentation ($78\% \pm 15\%$) achieved the highest mean scores, while applicability scored the lowest ($23\% \pm 18\%$). Inter-rater agreement was 0.74 (good) to 0.91 (very good). The most comprehensive CPGs were those developed by “National Institute for Health and Care Excellence” (NICE), International Menopause Society (IMS) and European Menopause and Andropause Society (EMAS).

Conclusions: Most menopause CPGs are poor to average quality with variation in EM/POI management recommendations. EM/POI management algorithms were developed from high scoring CPGs.

1. Introduction

Health professionals' knowledge gaps regarding menopause management have been identified and can potentially lead to variations in prescribing practices [1-3] including indications for menopausal hormone therapy (MHT) and duration of use [1]. Discrepancies between specialties and patients' uncertainties regarding management strategies [1, 4] highlight the importance of an evidence-based guideline to raise health professionals' awareness and provide care consistencies in clinical setting.

Clinical guidelines have become a major part of clinical practice over the last decades [5]. The ideal clinical practice guidelines (CPGs) are developed based on systematic reviews of the best scientific evidence [6]. They update clinicians with the most recent evidence and assist them in their clinical decisions [5], potentially leading to improved patient care through providing a consistent approach and the most appropriate treatment strategy [5]. Adherence to high quality CPGs can prevent the potential harms associated with using unnecessary medicine [5, 7] resulting in better health outcomes [8].

However, many CPGs published in different areas are limited by the paucity of high quality evidence and poor development methodologies [9-11] that could adversely impact the quality of patient care [5]. Implementation of the poor quality guidelines may also harm the healthcare systems in terms of wasting the limited resources and money [5]. To date, there are numerous CPGs on menopause management aiming to simplify clinical decision making for health professionals and improve the quality of care for midlife women. However, their methodological rigour and reliability are unknown and no previous quality assessment has been performed.

This study aimed to: 1) systematically search and evaluate the quality of CPGs of menopause management; 2) to identify menopause topics included in the CPGs; 3) to extract and summarize early menopause (EM) or premature ovarian insufficiency (POI) recommendations provided by high scored CPGs; and 4) develop EM/POI management algorithms.

2. Materials and methods

2.1. Search strategy

This review adheres to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The systematic search was conducted from June to July 2017 using relevant keywords in Medline, Medline IP, Embase and All EBM database (Appendix A). The search strategy was limited to the CPGs written in English and published between 2012 -2017. The following medical websites and specific guideline databases were also searched to identify any further guidelines: National Guideline Clearing house (NGC), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Canadian Clinical Practice Guideline (CPG), Turning Research Into Practice (TRIP) data base, North American Menopause society (NAMS), Australian Menopause Society (AMS), International Menopause Society (IMS), British Menopause society (BMS), US Endocrine Society, Royal Australian and New Zealand College of Obstetrician and Gynaecologist (RANZCOG), National Health and Medical Research Council (NHMRC) and European Society of Human Reproduction and Embryology (ESHRE).

A preliminary screening was performed through titles and abstracts of all citations by one reviewer (LY). Duplicate references and those not meeting the inclusion criteria were excluded from further review. Finally, full-text papers were assessed to ensure eligibility. All supplementary materials related to guidelines were also reviewed by all

appraisers. The review protocol is according to PRISMA statement and is available from

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017065630.

2.2. Eligibility criteria

The latest version of national and international CPGs on menopause management published in English between 2012 and 2017 were included. We excluded systematic reviews, randomized controlled trials (RCTs), pilot trials, observational studies and CPGs on the long-term implications of menopause such as osteoporosis or cardiovascular disease. In this study, we defined “CPG” to include published guidelines, recommendations, position statements, care pathways and consensus statements, as these are all intended to assist clinicians in management.

2.3. Quality assessment

Four appraisers (LY, JAB, AW, AJV) independently reviewed and evaluated the quality of guidelines using the Appraisal of Guidelines for Research & Evaluation II instrument (AGREE II). AGREE II is a standard instrument designed to appraise the quality of health related CPGs (Available from www.agreetrust.org).

It comprises 23 items with 6 domains: 1) scope and purpose (items 1-3); 2) stakeholder involvement (items 4-6); 3) rigour of development (items 7-14); 4) clarity of presentation (items 15-17); 5) applicability (items 18-21); and 6) editorial independence (items 22-23). The items within each domain are rated based on a 7-point Likert scale ranging from 1 for strongly disagree, when items are poorly reported, to 7 for strongly agree showing the exceptional quality of reporting. Scoring of 2-6 indicates that the full criteria have not been met. Scores increase as more criteria are met. Finally, there are two overall assessment items including the overall quality of the guideline and recommendation for use.

The total scores for each domain were calculated by summing up the scores of all items within each domain and then by scaling the total as a percentage of the maximum possible score for that domain. The scaled domain score was calculated through the following formula:

$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100$$

2.4. Assessment of CPGs recommendations

Menopause topics included in the guidelines were identified including diagnosis, symptoms, treatment strategies and risks/benefits of MHT. The most comprehensive guidelines were those that covered all menopause topics.

Also, EM/POI recommendations reported in high scored CPGs were summarized and used to develop an EM/POI management algorithm. Expert clinician feedback was used to refine the algorithm.

2.5. Data analysis

Inter-rater reliability was performed to assess agreement between reviewers using the Intraclass Correlation Coefficient (ICC) with a 95% Confidence Interval (CI). Appraisers discussed scoring when the ICC<0.70 [12] and disagreement resolved by consensus. The reliability analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0. Mean and standard deviation (SD) scores were calculated for each domain and the total score was calculated for each guideline using Microsoft Excel 2013. CPGs were considered high quality if 5 or more domains scored > 60%, average quality if 3 or 4 domains scored > 60%, and low quality if 2 or less domains scored >60% [12].

3. Results

3.1. Search results

A detailed diagram of the review process is shown in Figure 1. The initial search yielded a total of 1172 citations and 12 publications were found from other sources. Following the initial screening of the titles and abstracts, 57 potentially eligible CPGs were identified for full text review and finally a total of 22 CPGs were included for review.

3.2. Characteristics of CPGs

Table 1 shows the general characteristics of CPGs on menopause management. Of 22 CPGs, 3 were developed specially for women with EM/POI, 3 provided information regarding non-hormonal therapy for menopausal symptoms, 1 offered recommendations for hormone therapy in hysterectomized women, 1 included recommendations for women with breast cancer and the other 14 CPGs provided general recommendations for menopause management. Length of the guidelines varied from 3 to 283 pages. Guidelines have been published in different countries including USA (n=5), UK (n=5), European (n=4), Australia/New Zealand (n=2), Poland (n=1), Canada (n=1), South Africa (n=1), Spain (n=1), Sri Lanka (n=1) and various countries (n=1). CPG development groups included medical societies, government bodies and expert panels.

3.3. Methodological quality of CPGs

The mean scores of each domain, the total scores and the overall assessment for evaluated CPGs are shown in Table 2. Inter-rater agreement for the evaluation of guidelines were 0.74 (good; 95% confidence interval, 0.51-0.88) to 0.91 (very good; 95% confidence interval, 0.84-0.96).

Domain 1: Scope and purpose relates to the overall objective of the guideline, specific health questions and the target population. The mean score of this domain was 73% \pm 15% with only 3 guidelines scoring <60%. The NICE [13] and ESHRE [14]

guidelines scored the highest (99%), while the guideline developed by Sri Lanka Medical Association [15] obtained the lowest score (32%).

Domain 2: Stakeholder involvement refers to the extent that stakeholders were involved in the process of guideline development. The mean score of this domain was $40\% \pm 22\%$, range 10% to 92%. NICE [13](92%), ESHRE [14](81%) and Cancer Australia [16](78%) were the three highest scoring CPGs for this domain.

Domain 3: Rigour of development relates to the process of evidence synthesis, the methods of developing recommendations, updating and external review. NICE [13] and ESHRE [14] guidelines achieved the highest scores of 95% and 85%, respectively. The Global consensus statement [17] and recommendations for hysterectomized women [18] scored the lowest for this domain with 19%.

Domain 4: Clarity of presentation assesses the language, structure and format of the recommendations. The scores for all guidelines were generally high for this domain with a mean total score of $78\% \pm 15\%$. The UK- Consensus statement [19] and European Menopause and Andropause Society (EMAS)-non-hormonal guideline [20] received the lowest score of 50%.

Domain 5: Applicability focuses on the barriers and facilitators to implementation of the guidelines, how recommendations can be put in clinical practice, resource implications of applying the recommendations, and monitoring or auditing criteria. This domain achieved the lowest mean score of $23\% \pm 18\%$ (ranging from 5% to 83%) with 19/ 22 CPGs scoring <40%.

Domain 6: Editorial independence assesses whether the funding sources and competing interest of the guideline developers have been reported. The mean score for this domain was $58\% \pm 28\%$, with high scoring guidelines including ESHRE [14], NICE [13], US Endocrine Society [21], Spanish Menopause Society [22], EMAS-non-

hormonal [20] and UK-Consensus statement [19] scoring >80% compared with the Sri Lanka Medical Association guideline (0%) [15].

3.4. Overall assessment

The quality scores of guidelines ranged between 21% and 93%. According to the overall quality, 2 CPGs were considered “high quality”, 10 “average” and 10 “low quality”. High quality CPGs were those developed by NICE [13] and ESHRE [14] with mean scores of 93% and 85%, respectively.

3.5. Guideline Content

Guideline content varied in regard to menopause topics including diagnosis, symptoms, menopause management, MHT benefits/risks and POI. The most comprehensive CPGs were NICE [13], IMS [23] and EMAS [24] guidelines. Some CPGs focussed on a particular aspect on menopause management such as the NAMS [25], EMAS [20] and UK-Consensus statement [19] related to non-hormonal management. Of the three CPGs that specifically looked at non-hormonal management, the guideline developed by NAMS [25] was in average quality that performed well in scope and purpose, rigour of development and clarity of presentation domains (>60%), while the UK-Consensus statement [19] and EMAS [20] were not recommended to use. The guideline developed by Cancer Australia [16] focusing on menopause management in women with breast cancer effectively addressed 4 out of 6 domains, however, it requires significant modifications in applicability and editorial independence domains. Similarly, the guideline that targeted the hysterectomized women [18] was in average quality with significant limitations in stakeholder involvement, rigour of development and applicability.

3.6. Development of EM/POI management Algorithm

Three of the high scoring guidelines (ESHRE [14], NICE [13] and IMS [23]) were assessed in terms of EM/POI management recommendations. The ESHRE [14] guideline refers specifically to POI, but other CPGs provide recommendations related to peri/post menopause, and all used different grading systems for recommendations. The guidelines developed by the US Endocrine Society [21] and Cancer Australia [16], although high scoring CPGs, did not specifically refer to POI. A summary of the recommendations is shown in Table 3. POI diagnostic criteria varied where ESHRE [14] recommends a cut-off level of follicle stimulating hormone (FSH) > 25 IU/l whereas IMS [23] reports FSH \geq 40 IU/l, both based on expert consensus. ESHRE [14] and IMS [23] suggest karyotype, fragile X testing and auto-immune screening as the initial evaluation to assess the cause of EM/POI, however, no information was provided by other guidelines. All three guidelines agreed on indications for MHT and suggest prescribing MHT until the average age of natural menopause. However, there were inconsistencies regarding MHT regimen and the oral contraceptive pill (OCP) administration as an acceptable alternative with some guidelines not providing any recommendation in this regard. Androgen therapy was recommended for low sexual desire by ESHRE [14] and IMS [23], although both guidelines acknowledge the lack of evidence for long-term effects. ESHRE [14] advises behavioural modifications such as healthy weight, healthy diet, exercise and cessation of smoking to improve health, although evidence is limited.

The summaries from the three high ranked guidelines were used to develop diagnosis and management algorithms for early menopause with refinement using expert clinician feedback including endocrinologists, gynaecologists and primary care providers. Development of this algorithm is part of an overall project involving the

production of a co-designed online resource for women and health professionals regarding EM/POI which will facilitate implementation.

A summary management algorithm is shown in Figure 2. Separate diagnosis and management algorithms are available at:

https://www.monash.edu/__data/assets/pdf_file/0008/1515185/POI-diagnosis-evaluation-algorithm.pdf

https://www.monash.edu/__data/assets/pdf_file/0007/1515184/POI-management-algorithm.pdf

4. Discussion

This study is the first to evaluate the quality of CPGs of menopause management and also assess the consistency of EM/POI recommendations in high scoring guidelines. Our AGREE II evaluation indicates that most menopause guidelines are poor to average quality with significant limitations in many domains. Guidelines also vary regard to content and details of recommendations. Consensus was observed between high scoring guidelines for some EM/POI recommendations.

This study indicated wide heterogeneity regarding quality amongst menopause guidelines with only two guidelines developed by NICE [13] and ESHRE [14] meeting most AGREE II criteria. NICE guideline [13] consisting of a full version, a summary and appendices was recognized as the highest quality and the most comprehensive menopause guideline published over the recent five years. This guideline performed well in methodological quality and the scientific content. However, the length of this document with 283 pages and limited information on EM/POI, (although NICE was primarily designed as a general menopause CPG), were limitations that could be considered for updating and development of the future guidelines. Concerns have been expressed regarding reporting of risk estimates for MHT and information related to alternatives to MHT in NICE CPG [26]. However, this is disputed by the NICE

authors [27]. ESHRE [14] was also considered a high quality CPG but was specific to POI. Variations in the quality of CPGs can lead to confusion among clinicians and inconsistencies in management that potentially impact the quality of care and clinical outcomes [28, 29].

Consistent with previous systematic reviews of CPGs [9, 28, 30-32], scope and purpose (domain 1) and clarity of presentation (domain 4) received the highest quality scores, while the lowest score was noted for applicability (domain 5). Scope and purpose includes the key components of the guidelines (overall aim and target population) which is a recognised requirement. Clarity of presentation, demonstrating the least variability among guidelines, is also an obvious important characteristic for any CPG. However, the significant limitations identified in applicability for most CPGs indicates that strategies to facilitate implementation have not been addressed. NICE [13], ESHRE [14] and NAMS [33] were the only CPGs that discussed the potential resource implications. Previous evaluations of guidelines related to allergic rhinitis [34], infertility [35] and arthritis [11, 36] also received the lowest mean scores for this domain ranging from 14% to 37%. Applicability is the fundamental section of the guidelines that can lead to effective implementation of the recommendations in clinical practice, otherwise utilization of the guidelines would be limited despite high methodological quality [37]. NICE [13] was the only CPG with an implementation plan. Lack of implementation strategies would limit the widespread use of guidelines and prevent the desired outcomes regarding menopause care improvement from being achieved [38]. A current study evaluating the attitudes of health professionals regarding MHT reported that only 50% of the participants considered it easy to comply with the existing menopause management recommendations [1]. Indeed, conferences,

menopause society websites and journal articles were the preferred means of accessing the current evidence [1].

A majority of guidelines failed to use a rigorous methodology to develop CPGs. A rigorous approach in developing the guidelines in terms of the evidence synthesis, external expert reviews and future updates would be expected to increase the reliability of the guidelines. According to a systematic review on 118 guideline appraisal studies, rigour of development and applicability are the key domains that affect the final overall assessments of the guidelines [39].

Most guidelines failed to engage the appropriate stakeholders such as consumers, relevant clinicians, researchers, methodology experts and policy makers in the process of guideline development. The CPGs developed by NICE [13], ESHRE [14] and Cancer Australia [16] were the only guidelines that considered patients/public opinions and preferences in the process of development.

Funding sources and competing interests of guideline developers were poorly reported in some menopause CPGs. Previous studies indicate a high prevalence of potential conflict of interests and lack of disclosures among guidelines published in different areas [40, 41] which makes the guidelines susceptible to bias and potentially affect translation of evidence to clinical recommendations [42].

Content and recommendations regarding menopause management varied between guidelines. CPGs developed by NICE [13], IMS [23] and EMAS [24] addressed all major clinical topics of menopause such as diagnosis, symptoms, menopause management and POI, although the depth of discussion varied. Unsurprisingly, most general menopause guidelines lack detailed information on POI management as distinct from the ESHRE POI specific guideline. Menopause CPG recommendations relied upon evidence derived from predominately European and North American

studies raising the question of applicability to local settings. As such, research to address evidence gaps, development of multidisciplinary and globally collaborative POI specific CPGs are required.

Lack of high quality evidence has been the major barrier to developing clinical guidelines and limits the assessment of the clinical risks/benefits of different treatments [43]. EM/POI recommendations included in high scored CPGs including ESHRE [14], NICE[13] and IMS [23] differed in some aspects of menopause management. FSH diagnostic criteria for POI varied between ESHRE [14] and IMS [23] and were both based on expert consensus. All guidelines related to EM/POI were consistent on indications for MHT and acknowledge the need for MHT until the average age of menopause, but there were discrepancies on hormone therapy regimen, and OCP administration. This observed variation between guidelines reflects the lack of evidence to guide management of EM/POI and highlights the need for more research.

High quality CPG development is a demanding and expensive undertaking. To achieve consistency of recommendations and attain the ideal of an internationally accepted high quality menopause CPG, collaboration between medical societies, government and stakeholders is required with further research to inform the recommendations. CPG development should be followed by a country-specific implementation plan to optimize guidelines uptake in the clinical setting. This has recently been achieved for polycystic ovary syndrome [44].

4.1. Strengths and Limitations

The key strengths of this study were: 1- Use of an extensive search strategy to retrieve menopause guidelines, 2- application of AGREE II as a valid and reliable tool for guidelines evaluation, 3- Using multiple trained appraisers, and 4- achieving a high

level of agreement between reviewers in assessing guidelines. However, our review was limited to guidelines published in English language. Also, as reported by other studies [12, 45], AGREE II has some limitations: (1) It only appraises the guidelines in terms of the rigour of methodology and does not provide specific content assessment; and (2) Guideline appraisers may have different interpretation on the items and scoring system; however, to minimise this, we utilised the AGREE scoring guidelines and conducted inter-rater reliability assessment.

4.2. Conclusion

This study indicates significant deficiencies and variation in currently available menopause CPGs, including quality, content and recommendations, with only two guidelines recommended for use in clinical practice. We have co-designed an evidence-based algorithm from the highest quality guidelines, to facilitate clinical diagnosis and management of women with EM/POI.

Contributors

Ladan Yeganeh conducted the systematic search, screened search results, reviewed guidelines, extracted and analysed data and drafted the manuscript.

Jacqueline A Boyle contributed to study design, guideline review, data extraction, manuscript review and providing clinical expertise and supervision.

Anna Wood contributed to guideline review and data extraction.

Helena Teede contributed to study design, manuscript review and providing clinical expertise and supervision.

Amanda J Vincent contributed to study design, guideline review, data extraction, manuscript preparation, revision and editing and provided clinical expertise and supervision.

Conflict of interest

Jacqueline Boyle was a member of the Women's Health committee of Royal Australian and New Zealand College of Obstetrician and Gynaecology (RANZCOG). Amanda Vincent is a member of the editorial board of Climacteric which published the IMS CPG. There are no other conflicts of interests.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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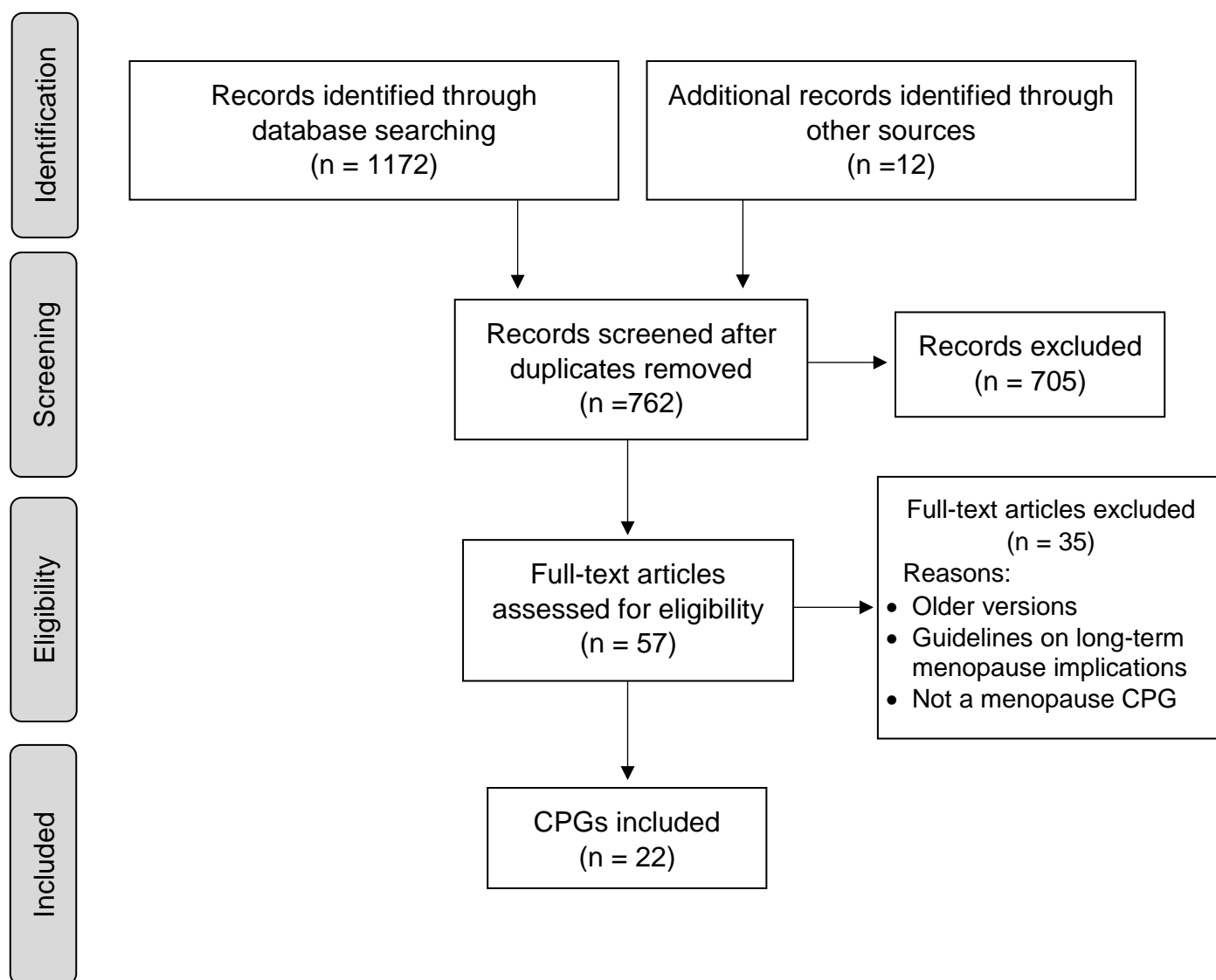


Figure 1.

Initial diagnosis and evaluation of POI cause		
POI diagnostic criteria	Evaluation to assess cause	Investigations
<ul style="list-style-type: none"> Oligo/amenorrhea for at least 4 months FSH levels >25 IU/l on 2 tests, at least 4–6 weeks apart (When not on any hormone therapy) 	<ul style="list-style-type: none"> Medical history + Examination <ul style="list-style-type: none"> General medical history Gynaecologic history + examination including pubertal development History of chemo/radiotherapy, pelvic surgery Symptoms and signs of autoimmune disorders Symptoms and signs of specific phenotype (eg. Turner syndrome) 	<ul style="list-style-type: none"> Non-iatrogenic POI (Consider autoimmune, genetic and infectious diseases) <ul style="list-style-type: none"> Karyotype testing Fragile X testing Antibody testing (Thyroid antibodies, 21 hydroxylase or adrenocortical antibodies, Other antibodies as indicated by history and examination) Pelvic / Vaginal Ultrasound

Evaluation for treatment and complication screening	
History and examination	Investigations
<ul style="list-style-type: none"> Cause of POI Symptoms Sexual function Osteoporosis risk factors CVD risk factors Psychological risk factors Fertility Pre-existing medical conditions BP/weight/height 	<ul style="list-style-type: none"> Renal function Liver function Bone: <ul style="list-style-type: none"> BMD test Vitamin D CVD: <ul style="list-style-type: none"> Fasting lipid profile Fasting plasma glucose or HbA1c

Management						
MHT <ul style="list-style-type: none"> Continuous combined MHT Cyclical combined MHT Combined OCP or LNG IUS + Oestradiol if contraception required Oestrogen-only MHT if hysterectomy 	Non-hormonal treatments for VMS <ul style="list-style-type: none"> SSRIs SNRIs Gabapentin / Pregabalin Clonidine (Evidence for older women only) 	Lifestyle management <ul style="list-style-type: none"> Cease smoking Regular exercise Healthy weight Diet Adequate Calcium intake Adequate Vitamin D Reduce alcohol intake 	Complementary therapy <ul style="list-style-type: none"> CBT Mindfulness Yoga Hypnosis (Evidence for older women only) Insufficient evidence to recommend herbal therapies/ complementary medicine 	Fertility <ul style="list-style-type: none"> refer to specialist 	Psychological <ul style="list-style-type: none"> Counselling Refer to psychologist /psychiatrist Refer to support group 	Bone health/CVD <ul style="list-style-type: none"> Manage risk factors Refer to specialist if bone loss or fracture/CVD



Monitoring
<ul style="list-style-type: none"> Continue MHT until the age of natural menopause Annual clinical review to assess MHT risks/benefits (CVD/ bone health/ other health issues as required) Mammogram as per national recommendations Cervical smear as per national recommendations Yearly TSH if positive thyroid antibody No specific recommendation regarding repeating autoimmune screening if initially negative BMD monitoring

Additional notes:

- Usual contraindications to OCP and MHT apply
- 17 β-E preferred to EE/CEE
- Higher dose may be required (eg. transdermal E, 75–100 µg, oral E ≥2mg/d)
- Cyclical combined MHT may be preferred (12 week cycle regimens long term safety unknown)
- Vaginal oestrogen if persisting urogenital symptoms on MHT
- Consider short-term use of testosterone patches/creams for sexual function (lack of evidence regarding long-term effects)

Abbreviations:

FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; CVD, cardiovascular disease; BP, blood pressure; OCP, oral contraceptive pill; LNG IUS, levonorgestrel intrauterine system; MHT, menopausal hormone therapy; E, oestradiol; EE, ethinyl oestradiol; CEE, conjugated equine oestrogen; VMS, vasomotor symptom; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin nor-epinephrine reuptake inhibitors; CBT, cognitive behaviour therapy; BMD, bone mineral density

Figure 2.

Table 1. General characteristics of menopause guidelines

Title	Focus of the guideline	Country	Year of publication	Organization	No. of pages
Guidelines for menopausal hormone therapy: Recommendations of the Polish Menopause and Andropause Society [46]	Menopause management	Poland	2014	Polish Menopause and Andropause Society	12
Management of the menopause [47]	Menopause management	Australia/New Zealand	2014	Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	11
Managing menopause [48]	Menopause management	Canada	2014	Society of Obstetricians and Gynaecologists of Canada	80
Management of menopausal symptoms [49]	Menopause management	USA	2014	American College of Obstetricians and Gynaecologists (ACOG)	15
South African Menopause Society revised consensus position statement on menopausal hormone therapy [50]	Menopause management	South Africa	2014	South African Menopause Society (SAMS)	11
Management of women with premature ovarian insufficiency [14]	POI	European	2015	European Society of Human Reproduction and Embryology (ESHRE)	161
Non-hormonal management of menopause-associated vasomotor symptoms [25]	Non-hormonal management	USA	2015	North American Menopause Society (NAMS)	18
Treatment of symptoms of menopause: An Endocrine Society Clinical Practice Guideline [21]	Menopause management	USA	2015	Endocrine Society	37
Menopause: diagnosis and management [13]	Menopause management	UK	2015	National Institute for Health and Care Excellence (NICE)	283
Spanish consensus on premature menopause [22]	POI	Spain	2015	Spanish Menopause Society, Spanish Fertility Society, and Spanish Contraception Society	6
Recommendations for hormone therapy in hysterectomized women: importance of new data in clinical management [18]	Hysterectomized women	USA	2015	No specific organization-The authors affiliate to Mayo clinic, USA	10
European Menopause and Andropause Society position statement: The ten point guide to the integral management of menopausal health [51]	Menopause management	European	2015	European Menopause and Andropause Society (EMAS)	5
EMAS position statement: Non-hormonal management of menopausal vasomotor symptoms [20]	Non-hormonal management	European	2015	European Menopause and Andropause Society (EMAS)	4
Caring for women in their post reproductive life: current recommendations on hormone replacement therapy [15]	Menopause management	Sri Lanka	2015	Sri Lanka Medical Association	4
Management of menopausal symptoms in women with a history of breast cancer [16]	Breast cancer	Australia	2016	Cancer Australia	181
2016 International Menopause Society Recommendations on women's midlife health and menopause hormone therapy [23]	Menopause management	UK	2016	International Menopause Society (IMS)	43
Maintaining post reproductive health: A care pathway from the European Menopause and Andropause Society (EMAS) [24]	Menopause management	European	2016	European Menopause and Andropause Society (EMAS)	10
The British Menopause Society & Women's Health Concern 2016 recommendations on HRT in menopausal women [52]	Menopause management	UK	2016	British Menopause Society (BMS)	19
Revised global consensus statement on menopausal hormone therapy [17]	Menopause management	-	2016	* Various organizations	3
Consensus statement for non-hormonal-based treatments for menopausal symptoms [19]	Non-hormonal management	UK	2017	No specific organization- The author affiliates to Clementine Churchill Hospital, UK	5
The 2017 hormone therapy position statement of The North American Menopause Society [33]	Menopause management	USA	2017	North American Menopause Society (NAMS)	26
The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency [53]	POI	UK	2017	British Menopause Society (BMS)	14

Note: International Menopause Society, North American Menopause Society, Endocrine Society, European Menopause and Andropause Society, Asia Pacific Menopause Federation, International Osteoporosis Foundation, Federation of Latin American Menopause Societies. Guidelines are presented in publication order.

Table 2. Domain scores and overall assessment of menopause guidelines using the AGREE II instrument

Clinical Practice Guideline (Name of organization)	Domain 1 (%)	Domain 2 (%)	Domain 3 (%)	Domain 4 (%)	Domain 5 (%)	Domain 6 (%)	Total score Mean (SD) (%)	Overall quality	Overall recommendation
NICE [13]	99	92	95	97	83	92	93 (6)	High	Recommended
ESHRE [14]	99	81	85	97	50	98	85 (19)	High	Recommended
Endocrine Society [21]	81	36	67	92	40	94	68 (25)	Average	With Modification
Cancer Australia [16]	90	78	79	88	23	42	67 (28)	Average	With Modification
IMS [23]	74	42	48	96	31	69	60 (24)	Average	With Modification
The Society of O&G of Canada [48]	89	46	65	92	38	21	59 (29)	Average	With Modification
NAMS-hormone therapy [33]	67	40	55	86	28	69	58 (21)	Average	With Modification
NAMS-NH [25]	75	39	63	89	23	54	57 (24)	Average	With Modification
RANZCOG [47]	72	63	52	85	19	31	54 (25)	Average	With Modification
EMAS- A care pathway [24]	78	35	27	76	19	73	51 (27)	Average	With Modification
Spanish Societies [22]	64	31	34	72	13	85	50 (28)	Average	With Modification
Mayo clinic, USA- Hysterectomized women [18]	67	17	19	65	11	67	41 (28)	Average	With Modification
ACOG [49]	86	33	52	81	17	27	49 (29)	Low	Not recommended
BMS- HRT [52]	51	19	28	85	21	77	47 (29)	Low	Not recommended
SAMS [50]	68	26	33	82	19	48	46 (25)	Low	Not recommended
EMAS-NH [20]	81	26	25	50	10	81	46 (30)	Low	Not recommended
Global consensus statement [17]	69	47	19	93	5	35	45 (32)	Low	Not recommended
EMAS- The ten point guide [51]	71	42	21	54	10	67	44 (25)	Low	Not recommended
BMS-POI [53]	68	18	23	71	6	60	41 (29)	Low	Not recommended
Polish Menopause and Andropause Society [46]	71	40	20	68	32	6	40 (26)	Low	Not recommended
Clementine Churchill Hospital, UK-Consensus statement [19]	58	11	22	50	10	83	39 (29)	Low	Not recommended
Sri Lanka Medical Association [15]	32	10	20	57	7	0	21 (21)	Low	Not recommended
Mean (SD) (%)	73 (15)	40 (22)	43 (24)	78 (15)	23 (18)	58 (28)			

Note: **NICE**, National Institute for Health and Care Excellence; **ESHRE**, European Society of Human Reproduction and Embryology; **IMS**, International Menopause Society; **O&G**, obstetricians & Gynaecologists; **NAMS**, North American Menopause Society; **NH**, non-hormonal; **RANZCOG**, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; **EMAS**, European Menopause and Andropause Society; **ACOG**, American College of Obstetricians and Gynaecologists; **BMS**, The British Menopause Society; HRT, hormone replacement therapy; **SAMS**, South African Menopause Society; **POI**, premature ovarian insufficiency

Table 3. Summary of recommendations for Diagnosis and initial evaluation of early menopause (EM) / premature ovarian insufficiency (POI)

Guidelines	Diagnostic criteria	Initial evaluation				
		Karyotype	Fragile-X	Autoimmune screening	CVD	Bone health
ESHRE	<ul style="list-style-type: none"> • Oligo/amenorrhea for at least 4 months • FSH level > 25 IU/l on two occasions > 4 weeks apart (GPP) 	Yes (C)	Yes (B)	Yes (C)	Yes	Yes
		<ul style="list-style-type: none"> • If Turner syndrome: Further evaluation for co-morbidities • If Y chromosome: Gonadectomy (C) 	If detected then refer to geneticist	<ul style="list-style-type: none"> • Adrenal antibodies Positive: Refer to an endocrinologist for testing of adrenal function and rule out Addison's disease (C) Negative: Re-test in case of clinical signs or symptoms (C) • Thyroid antibodies Positive: Test TSH every year (C) Negative: Re-test in case of clinical signs or symptoms (C) 	<ul style="list-style-type: none"> • BP • weight (GPP) <p>If Turner syndrome: In addition to the above,</p> <ul style="list-style-type: none"> • Lipid profile • Fasting plasma glucose • HbA1c (C) 	<ul style="list-style-type: none"> • DXA (C) <p>If osteoporosis: DXA should be repeated within 5 years (GPP)</p>
NICE	<ul style="list-style-type: none"> • Menopausal symptoms • No or infrequent periods • Elevated FSH levels on 2 blood samples 4–6 weeks apart. 	No details	No details	No details	No details	No details
IMS	<ul style="list-style-type: none"> • Menopausal symptoms • Oligo/amenorrhea • FSH level ≥40 IU/l on two occasions at least 4–6 weeks apart (GPP) 	Yes (GPP)	Yes (GPP)	Yes (GPP)	No details	Yes DXA-optional (GPP)

Note: ESHRE, European Society of Human Reproduction and Embryology; NICE, National Institute for Health and Care Excellence; IMS, International Menopause Society; FSH, follicle stimulating hormone; GPP, good practice point; CVD, cardiovascular disease; BP, blood pressure; DXA, Dual-energy X-ray absorptiometry; TSH, thyroid stimulating hormone. **Grading of evidence:** ESHRE: A, B, C, D, GPP[14] ; NICE: Very low, low, moderate, high[13] ; IMS: 1++, 1+, 1-, 2++, 2+, 2-, 3, Grade: A, B, C, D [23].

Table 4. Summary of recommendations for early menopause (EM) / premature ovarian insufficiency (POI) management

Guidelines	MHT	Indications for MHT	Duration of MHT (until 50 yrs)	MHT regimen	Monitoring of MHT	OCP	Androgen therapy	Lifestyle/complementary therapy
ESHRE	Yes (C)	<ul style="list-style-type: none"> • VMS ☑ • Urogenital symptoms☑ • Sexual function ☑ • Bone health ☑ • CVD ☑ • Neurological function☑ (C) 	Yes	<ul style="list-style-type: none"> • Cyclical combined MHT is preferred (GPP) • Cycle no longer than 12- weeks • 17 β-E is preferred to EE or CEE (C) • Systemic & local MHT for sexual function & urogenital symptoms (C&D) • Combined MHT if intact uterus (B) • E-only MHT if absent uterus 	<ul style="list-style-type: none"> • Annual clinical review (GPP) • Mammographic screening as normal population 	<ul style="list-style-type: none"> • Appropriate for some women • Less beneficial effects on BMD (C) 	<ul style="list-style-type: none"> • Low sexual desire • Short-term use of T patches • Lack of evidence on long-term effects (C) • Treatment effect evaluated after 3-6 months and limited to 24 months (GPP) 	<ul style="list-style-type: none"> • Not smoking • Regular exercise • Healthy weight • A balanced diet (GPP) • Insufficient evidence
NICE	Yes	<ul style="list-style-type: none"> • VMS ☑ • Urogenital symptoms • Sexual function • Bone health ☑ • CVD ☑ • Neurological function 	Yes	No details	No details	<ul style="list-style-type: none"> • Insufficient evidence to show whether HRT or the combined OCP is more effective • Considering women's preferences and needs 	No details	No details
IMS	Yes (B)	<ul style="list-style-type: none"> • VMS ☑ • Urogenital symptoms☑ • Sexual function ☑ • Bone health ☑ • CVD ☑ • Neurological function☑ 	Yes (B)	<ul style="list-style-type: none"> • Higher doses of estrogen • 17 β-E, 2 mg/day or 1.25mg CEE or transdermal E, 75–100 μg/day or 10 μg EE • Micronized progesterone, cyclic regimen (200mg for 12 days/month), continuous regimen (100mg/day) >2 years post-menopause 	No details	<ul style="list-style-type: none"> • Combined OCP may be used continuously until the expected time of the menopause • Bone and metabolic effects are more favourable with MHT compared to OCP (1-) (Data are lacking) 	<ul style="list-style-type: none"> • In women with low libido, T gels/patches (2++) 	No details

Note: VMS, vasomotor symptom; CVD, cardiovascular disease; MHT, menopausal hormone therapy; OCP, oral contraceptive pill; E, oestradiol; EE, ethinyl oestradiol; CEE, conjugated equine oestrogen; GPP, good practice point; BMD, bone mineral density; T, Testosterone; **Grading of evidence:** ESHRE: A, B, C, D, GPP[14] ; NICE: Very low, low, moderate, high [13]; ; IMS: 1++, 1+, 1-, 2++, 2+, 2-, 3, 4, Grade: A, B, C, D [23].

Appendix A. Search Strategy:

- 1 guideline*.ti.
- 2 practice guideline*.ti.
- 3 clinical practice guideline*.ti.
- 4 clinical guideline*.ti.
- 5 guidance*.ti.
- 6 clinical protocol*.ti.
- 7 recommendation*.ti.
- 8 care pathway*.ti.
- 9 consensus statement.ti.
- 10 critical pathway.ti.
- 11 exp consensus development conference/
- 12 Health Planning Guidelines/
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
- 14 menopaus* hormon* therapy.mp.
- 15 exp Hormone Replacement Therapy/
- 16 (hormon* adj therapy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 17 (hormon* adj treatment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 18 (menopaus* adj2 management).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 19 exp Menopause/

- 20 Primary Ovarian Insufficiency/
- 21 premature ovarian insufficiency.mp.
- 22 early menopause.mp.
- 23 premature ovarian failure.mp.
- 24 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
- 25 position statement*.ti.
- 26 13 or 25
- 27 24 and 26
- 28 limit 27 to (english language and yr="2012 - 2017")

Chapter 4: Translation with health resource development

4.1. Introduction

Consumers are increasingly becoming involved in healthcare decisions and require easy access to evidence-based information to inform their treatment choices (96). However, women report insufficient access to information about menopause and limited choices (5, 81). Online health information is becoming a regular part of patient care (97, 98) and is perceived as the best source of information by women with POI (75). High-quality resources can raise women's awareness and potentially lead to improved self-management and QoL (99). However, evidence indicates significant deficiencies and variation in the content and quality of the currently available menopause online resources (5, 77).

Interventions that provide patients with the most relevant information can motivate and engage them to positively adapt their behaviors and develop skills to better manage disease (100). One way to facilitate provision of patient's information is to use a QPL (101). A QPL is a structured list of questions which patients may wish to ask HPs and is designed to empower them to participate during health care appointments and obtain information relevant to their needs (101). These communication aids have been shown to significantly increase question-asking and consumer satisfaction, without affecting anxiety or the length of consultations (102-104). QPLs can suggest questions that patients had not previously thought about or offer difficult questions that patients may feel hesitant to ask (72). There are QPLs published in different areas including cancer (105, 106), palliative care (107), attention deficit hyperactivity disorders (ADHD) (108), and polycystic ovary syndrome (PCOS) (72); however, there is currently no QPL for EM/POI.

Discrepancies among specialties regarding menopause management (4) highlight the importance of a practical clinical guide based on the existing CPGs to raise HPs' awareness and provide care consistencies in the clinical setting. A management algorithm is an evidence-based guide which provides HPs with the most recent information in a user-friendly and easy access format. It would assist HPs to diagnose and decide the best treatment approach as per the women's needs and preferences and improve consistency in health care (109, 110). However, there is currently no management algorithm developed based on the recent EM/POI recommendations.

Here I led the co-design of novel online resources including an EM QPL for women and a management algorithm for HPs offering evidence-based information related to EM/POI. Current best practice in the development of healthcare resources involves a co-design approach which actively involves patients in the development process (111, 112) as this contributes to improved patient understanding and knowledge (113).

The final version of the EM/POI resources are freely available on the Healthtalk Australia website and MCHRI website:

www.healthtalkaustralia.org

<https://www.monash.edu/medicine/sphpm/mchri/research/themes/womens-and-childrens-public-health/early-menopause-research>

4.2. Development and evaluation of an early menopause question prompt list.

Summary

This study aimed to co-develop an early Menopause (EM) QPL and assess its acceptability and feasibility. This study consisted of three phases: (i) a survey to inform QPL development, (ii) interviews to explore acceptability and (iii) clinical pilot-testing to assess feasibility. The findings showed that women with EM have unmet information and communication needs, and are supportive of a comprehensive EM QPL. The EM QPL was perceived as an acceptable and feasible resource for women to use during medical consultations. The QPL may help to meet the information needs of women with EM.

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Title Page

Development and evaluation of an early menopause question prompt list

Running title: Development of an early menopause QPL

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Abstract

Objective:

A question prompt list (QPL), a structured list of questions, assists women in acquiring relevant information and facilitates communication with healthcare providers (HPs). This study aims to co-develop an early Menopause (EM) QPL and assess its acceptability and feasibility.

Methods: This three phase study consisted of a survey to inform QPL development, interviews to explore acceptability and clinical pilot-testing to assess feasibility. Participants included: 263 survey respondents with EM, 18 women interviewed, and 11 women and 6 HPs in pilot-testing. Main outcome measures were: Survey: perceptions regarding communication with HPs, likeliness to use a QPL and QPL topics; Interviews: QPL user-friendliness and acceptability; Pilot study: women's QPL use, perceived helpfulness and future use, and HPs' perceived acceptability. Data analysis included descriptive statistics, logistic regression and thematic analysis.

Results: Women's perceived communication difficulties most commonly related to sexual function (50.6%), vaginal/urinary symptoms (43%) and psychological effects (41.1%). Most women (67.3%) indicated they were very likely to use an EM QPL. EM symptoms, effects and management were considered very important/essential QPL topics (>80%). Interviewed women perceived the QPL as comprehensive, user-friendly, informative and empowering. Most pilot study women asked 1-2 questions (73%), perceived the QPL as helpful (100%) and would use it again (81.8%). HPs reported that the QPL helped patients to ask questions and initiate discussion about important and sensitive issues.

Conclusions: Women with EM have unmet information and communication needs, and are supportive of a comprehensive EM QPL. The EM QPL was perceived as an acceptable and feasible resource for women to use during medical consultations.

Key words: Early menopause; question prompt list; co-design; information; communication

Introduction

Early menopause (EM) (menopause before 45 years) occurs spontaneously or secondary to medical treatment and affects over 10% of women (1). It is associated with significant health implications that may adversely impact quality of life (1). EM diagnosis is often delayed due to lack of knowledge amongst women and health professionals (HPs), leading to suboptimal management (2-4). Women are generally dissatisfied with the information and support provided by HPs (5, 6). Lack of accurate and reliable information may influence patient experience including illness perception, care satisfaction and health outcomes (7).

There is an increasing emphasis on patient engagement and participation in healthcare interactions and shared decision making (8). Patients who are more involved in information seeking are able to provide HPs with more details regarding their health condition (9). However, a recent study in women with chronic conditions reported that women have difficulty communicating with HPs during medical consultations (10). This indicates a need for evidence-based resources to improve patient centred care, evidence-based care, and health outcomes.

A question prompt list (QPL) is a structured list of questions for women to ask HPs, designed to encourage participation during health care appointments and help people obtain information relevant to their needs (11). QPLs may improve communication between women and HPs and facilitate shared decision making (11, 12). They have been reported to reduce anxiety, increase women's satisfaction (13, 14) and facilitate knowledge access and self-health management (10).

QPLs have been developed for various conditions including cancer (15-17), palliative care (11, 18), polycystic ovary syndrome (PCOS) (10), attention deficit and hyperactivity disorder (ADHD) (19), but not EM. This study aimed to: 1) assess the perspectives and information needs of women with EM to inform the development of an EM QPL, 2) explore EM QPL acceptability, 3) assess EM QPL feasibility.

Methods

Methodology previously used for the PCOS QPL (10) was adapted for the EM QPL. The study was conducted from May 2017 to February 2019. The eligibility criteria were age >20 years, formal diagnosis of EM, living in Australia and English literacy. Informed consent was obtained from all participants. This study consisted of three phases (Fig. 1). Each phase of this study was approved by the Monash Health Human Research Ethics Committee (Project number: 07062A).

Phase 1: Survey to inform QPL development

This survey (Supplemental Digital Content (SDC) 1) was performed to identify women's likelihood of using an EM QPL, themes and questions for inclusion in the QPL and the

preferred QPL format. Women with self-reported diagnosis of EM were recruited from a range of sources including hospital clinics, support groups, menopause society websites and cancer websites, and invited to participate in an online or paper survey. Survey questions were adapted from previous studies (3, 10, 20). Data regarding demographics, medical history, perceptions towards communication difficulties and QPL use and topics to include in a QPL were collected. A univariate or multivariate logistic regression model was used to measure the associations between likelihood of using a QPL and age, location, education or time since diagnosis. Data analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0.

Development of QPL content

A list of possible questions was compiled (by L.Y. and A.J.V.) using the survey results, existing patient and HP information sheets (Australasian Menopause Society, Jean Hailes Foundation for Women's Health) and menopause guidelines (21-24). A panel of expert clinicians (see Fig 1) provided feedback regarding the initial questions to ensure all relevant topics were covered. The major concerns of HPs were the number of questions included in the QPL and time constraints in the consultation. In order to mitigate this potential barrier, instructions on the front page of the QPL were included to ask women to prioritise their questions at each appointment.

The initial QPL (version 1) comprised instructions for use and questions subdivided into key areas: cause, diagnosis, symptoms, long-term health effects, management and support groups.

Phase 2: Interviews to explore QPL acceptability

QPL version 1 was tested using semi-structured individual (in person or telephone) and group interviews of women with EM, recruited from the same sources as phase 1. The interview guide was developed by authors (L.Y. and A.J.V.) based on a previous PCOS QPL study (10) and enquired about the length, format, content/language, ease of use, feeling towards QPL, the preferred time to receive and suggestions to improve (SDC 2). The QPL was then revised according to participant feedback and a consensus discussion between authors (L.Y., A.J.V., J.A.B. & H.T.). A list of links to evidence-based online menopause resources was also added and QPL version 2 was created. Women were encouraged to view the suggested websites prior to their appointment for answers to general questions.

A second different cohort of women were interviewed to test the QPL version 2. Patient recruitment and interviews proceeded until data saturation was reached (no new themes emerged) (25). Transcripts were thematically analysed by two independent researchers (L.Y. and N.N.K.) using NVivo version 12 (QSR-International, Melbourne, Victoria, Australia). The revised QPL was converted into an online downloadable print form (version 3). The fully

formatted pdf (version 4) is 19 pages long and includes 2 parts related to the questions and links to the online information.

Phase 3: Pilot-testing to assess QPL feasibility

Eligible women attending the Monash Health Menopause Clinic in January and February 2019 were invited to pilot-test the QPL. Eligible women were identified from the clinic appointment list and sent an invitation letter explaining the study and also a paper copy of the QPL (version 3) a week prior to their consultation. Women were asked to read the QPL and to use it during their upcoming consultation if they wished. On the day of their consultation, women were asked to complete a post-consultation questionnaire exploring the feasibility of the QPL. The questionnaire asked for demographics, QPL use, whether it was useful and helpful, willingness to use in future appointments and the preferred mode of access (Supplemental Digital Content 3). Additionally, HPs involved in consultations with participating women were asked to complete a post-consultation questionnaire regarding their views of the usefulness and barriers of using the QPL during a clinical consultation (Supplemental Digital Content 4).

Across all phases, categorical variables were reported as numbers/percentages. Continuous data were reported as mean and standard deviation (SD). The online survey, interview guide and pilot phase questionnaires are available as supplemental information. The final version of the QPL is freely available on the Healthtalk Australia EM website: <https://healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/overview-womens-experiences/resources-and-information-for-women/#a1>.

Results

Characteristics of participating women are shown in Table 1.

Phase 1: Survey to inform QPL development

From 386 returned questionnaires, 263 were suitable for analysis: 109 respondents did not have a formal diagnosis of EM, three did not live in Australia and 11 provided incomplete responses. Mean age of respondents was 53.81 ± 10.68 and the majority were diagnosed with EM at least 5 years ago (78.3%), lived in metropolitan area (55.6%) and had a post-school qualification (71.2%) (Table 1).

Most women (67.3%) would be likely to use an EM QPL during consultations and 63% considered a QPL as useful to include in an EM website. Women reported greatest difficulty communicating with HPs about sexual function (50.6%), vaginal/urinary symptoms (43%) and psychological effects (41.1%) (Fig. 2A). Over 80% of women considered symptoms, physical/psychological effects, long-term implications and management very important/essential to include in a QPL (Fig. 2B). Older age was associated with being less likely to use a QPL (OR, 0.96, 95% CI, 0.93-0.98, $p=0.004$). The odds of likelihood to use a QPL was increased amongst women with undergraduate diploma/vocational qualifications

compared to those who did not complete post-secondary education (OR, 2.07, 95% CI, 1.02-4.20, $p=0.04$). There were no significant associations between likelihood to use QPL and location (metropolitan versus rural/regional), or time since EM diagnosis (Supplemental Digital Content 5: Supplemental Table 1).

Phase 2: Interviews to explore QPL acceptability

Eighteen women were interviewed, 12 reviewed QPL version 1 and 6 reviewed version 2. Mean age of interviewed women was 52.41 ± 11.42 years, educational attainment was undergraduate diploma or less in 82.30% and 82.4% were diagnosed with EM 5 or more years ago with iatrogenic EM (52.9%) as the commonest cause of EM (Table 1). Thematic analysis of the interviews identified six major themes: general attributes and impressions, helpfulness, feelings towards QPL, using QPL with HPs, mode and time of access, suggestions for further development.

General attributes and impressions. Women perceived the QPL as informative, and encompassed a wide range of topics on EM applicable over their lifespan. Women felt that the QPL was well-structured, easy to understand language and was generally user-friendly. Although most participants mentioned that the QPL was a long document, they felt it was necessary in order to ensure comprehensiveness. The QPL also appeared to prompt awareness of issues that women had not considered previously and most considered using it during future medical consultations.

"It did prompt me to think about my risks and other things as I am getting older, like heart and cardiovascular and other bits and pieces" (P11). I've learned something about Alzheimer's and oestrogen, which I didn't really know (P4). Women also viewed the links as a prompt to achieve more information. *"Well, I actually found it quite interesting because there's a couple of links that I pushed on to because there's still information" (P1).*

Helpfulness. Women reported that the questions were relevant to their needs and informative. It would prompt them to ask questions and express their actual concerns and remind them the questions they need to ask.

"It educated me a lot because there was a lot of things ... which I didn't think or associate with menopause...I know that I struggle with memory quite a bit...But I never in the past connected it with menopause" (P12). "I liked the way it covered sex and things like that which is things that nobody ever talks about" (P5).

However, some sections were found irrelevant by those women related to their cause of EM or the time since diagnosis. *"It's reinforcing of what I already knew, because I have been going through 35 years of early menopause..., at this stage, ...some of these things are less relevant now" (P7).*

Feelings towards QPL. Women expressed mostly positive feelings towards the QPL such as 'interested', 'curious', 'informed', 'empowered', 'reassured', 'relieved' and 'impressed'. Some

women reported that they were insufficiently informed regarding EM at the time of diagnosis many years ago and wished that they had access to a resource like this. *“I wish I had had this at the time of my diagnosis, because there is so much I didn’t think of” (P9).* *“It would have made a world of difference if I had this twelve years ago” (P8).*

Initially, some women felt overwhelmed when reading the QPL, however ultimately felt that all questions were necessary to be incorporated in the QPL. Feelings of stress and anxiety were not reported by any women.

Using QPL with HPs. Women wished to use QPL with a range of HPs including general practitioners (most commonly mentioned), endocrinologists, oncologists and surgeons.

Mode and time of access. Most women preferred to access the QPL online, as it provides the possibility of printing the relevant sections and to review it prior to their consultation.

A few others preferred to access the QPL through a mobile app. In terms of their health journey, women preferred to receive the QPL as early as possible to be better informed. *“The sooner you can get this in front of someone, the better they will feel about understanding what changes they are seeing in themselves and why” (P7).*

Suggestions for further developments. The major suggestions were addition of questions, removing or modifying some questions, abridging the content and addition of web-links, hyperlinked index for electronic version and a glossary of terms (Supplemental Digital Content 6: Supplemental Table 2).

Women who reviewed QPL version 1 suggested to add website links, as they provide useful information and relieve their stress. They also wanted to include more questions related to vasomotor symptoms (VMS), urinary /sexual function, breast cancer, induced menopause, bone health, and hormone therapy (HT) indications/contraindications. For QPL version 2, women suggested the inclusion of questions related to psychological effects of EM, menopause management and sexual function. Some women suggested including a section that is more specific to their cause of EM.

Women also suggested that the website links be grouped in a separate section to make the document more user-friendly. *“There were so many links to different web pages that was at the start, like directly under the heading, it looks quite confusing to me...I’d want all the questions together” (P1).* *“Maybe the websites don’t need to be on this document and that could be a way to keep it shorter” (P2).*

Phase 3: Pilot-testing to assess QPL feasibility

Eleven out of 15 eligible women who attended the clinic, agreed to use the QPL during their EM related appointment and completed the post-consultation questionnaire. Of the four women who did not participate, three did not have sufficient time to read the QPL and one was not interested in participating. The mean age of participants was 38.64 ± 10.26 . Most

women lived in metropolitan area (81.8%), high school educational attainment (54.5%) and were diagnosed with EM at least 5 years ago (63.6%).

All women read the QPL before their consultation but only two women (18%) viewed the websites listed in the QPL. Most women (73%) asked 1-2 questions while 27% asked several questions. Women reported that the QPL was helpful, prompted them to ask questions and assisted them to put their concerns into words and discuss difficult/sensitive issues. Two patients (18%) felt that some questions in the list made them anxious. However, most reported that they would use it during their future appointments (81.8%) (Table 2). Over half of the participants believed that the QPL was the right length and 27% reported that it was too long but contained the required information. Most women (73%) preferred to receive the QPL prior to their consultation.

HPs feedback on QPL from pilot study

Six HPs (four gynaecologists and two endocrinologists) consulted with 11 women and feedback was received for eight consultations. HPs agreed that all women used the QPL during the consultations. They felt that the QPL helped patients to ask questions and discuss sensitive issues. Four HPs reported that the QPL facilitated communication with the patient and one perceived the QPL as unhelpful. Only two HPs indicated that the QPL prolonged or interfered with the flow of the consultation.

Discussion

To our knowledge, this study is the first to develop a QPL for women who experience EM and evaluate its acceptability to women and its feasibility for clinic use. The survey phase of this study showed that many women have difficulty communicating with HPs regarding various aspects of EM and support the idea of developing a QPL that includes a full range of EM features. Women who were interviewed perceived the QPL as a user-friendly, comprehensive and informative tool which empowered them to ask questions and raise their concerns. The feasibility of the QPL was also endorsed by women and HPs in the clinic setting.

Studies in other health settings report that patients may not know what to ask or how to express their concerns during medical consultations (10, 11). In our survey, women expressed difficulties raising concerns related to their sexual and psychological health. Post-menopausal women aged over 45 years have also reported difficulty discussing these topics (26). Ineffective communication has been identified as a barrier to treatment adherence and patient satisfaction potentially leading to negative outcomes (27). Therefore, interventions to promote communication skills should be a key component of clinical care to address women's needs and improve health outcomes and experiences of care (28). Various self-management approaches have been introduced to improve patients' communication and enhance their ability to participate in health care. A QPL is an acceptable tool that may assist patients initiate

conversation with HPs focusing on their information needs and can optimize health management (10).

Following the interviews and QPL testing in the clinic, women believed that this resource would encourage them to share concerns and discuss difficult or sensitive issues. We found that the EM QPL can facilitate question asking and encourage greater engagement with HPs regarding EM discussions. In line with a previous study (29), most women perceived the QPL as relevant and helpful and planned to use it during their next EM related appointments. A well-designed and relevant QPL may lead to increased information provision by clinicians (30, 31). In the interview process, women reported that the QPL would remind them of the questions they want to ask their HPs. In a systematic review on the effect of QPL on women seeking cancer treatment, knowledge recall was also improved with using the QPL during medical consultations (12).

Implementation strategies including clinical endorsement are important in promoting QPLs. In a multi-centre study in an oncology setting, all clinicians and majority of patients found the QPL very useful and practical, however, the lack of time and high workload of staff were the main barriers to the clinical distribution and implementation of the QPL (29). Multiple factors can facilitate implementation of the QPL which include improving patients' understanding of the QPL, providing resource access via online and paper formats, as well as clinical discussions regarding the dissemination options (29). Clinicians' endorsement of the QPL, has been also a key criterion affecting QPL utilization in routine care (14). Some studies showed no increase in total questions asked, if the QPL is not actively endorsed by physicians (32). In the present study, women reported that they would prefer to receive the QPL prior to their appointment. However, despite receiving the QPL one week earlier, none of the women had reviewed the QPL before their consultation. Providing the QPL in a different format (eg. website or app) may facilitate pre-consultation access to the QPL and also online information via the web-links. HPs in the Menopause clinic, a specialist outpatient setting, were supportive of QPL use; however, this may vary in other clinical settings.

Consistent with the existing literature (29, 33), most women felt it was best to receive the QPL at the time of or shortly after diagnosis. Question asking seems to be highest at the time of diagnosis as women wish to know more about the disease, prognosis and treatment. Women with longer duration since EM diagnosis found the QPL less relevant, as they potentially had less unmet information needs. Nonetheless, they felt that this would have been a useful resource to have had access to at the time of diagnosis. This reflects a need to make the QPL accessible as close to diagnosis as possible. Also, considering women's unmet information needs regarding EM (34), early access to the QPL could potentially increase women's awareness of the short and long-term implications of EM and enable women to apply appropriate prevention strategies.

There are inconsistent findings regarding the effect of a QPL on anxiety. Most studies found no effect or less anxiety with using the QPL (10, 19, 32) and reduction in anxiety was associated with increased satisfaction with the consultation (13). In a systematic review exploring the effectiveness of QPL interventions in oncology, positive psychological effects were observed (12). However, in this pilot study, two women reported that the QPL caused them to feel anxious.

The effect of QPLs on consultation length is ambiguous. Although many studies report no increase in consultation time when using QPLs (35), some others have mentioned an average increase of 8 to 33 minutes (32, 36). However, our pilot study suggested that the length of consultation was not increased with using the QPL. Most HPs also did not feel that the QPL impacted on the length or flow of the consultation. The number of questions in the QPL may impact consultation time (12). The length of the QPLs in other areas of health, vary from 10 to 50 pages (10, 17, 33, 37). In interview and pilot phases of this study, the majority of women felt that the length of the EM QPL (including 19 pages), was appropriate.

Strengths and Limitations

The key strengths of this study were: 1) using quantitative and qualitative studies to develop the QPL and identify its acceptability, 2) the novelty of research developing an EM QPL and assessing the views of both women and HPs, and 3) including women with a broad age range (35). However, this study includes several limitations. The findings may be less relevant to non-English speakers, women with lower literacy/ educational attainment and those without internet access. Most of the survey and interview participants had post-school qualifications which may affect the readability of the QPL. However, most women in the QPL pilot-testing were less educated (year 12 or less) and did not experience difficulties understanding the QPL. Providing a hard copy format of the QPL in the clinic for pilot-testing would have limited access to the included online information. Self-reported diagnosis of EM was another limitation of this study. Given the nature of the pilot study (a small sample single group trial), we were unable to assess the effect of the intervention on the number of questions asked, the length of the consultation and anxiety scores. A broader engagement of women in different clinical settings to address limitations and also conducting a randomized controlled trial with a larger sample size for further evaluation of the QPL would be appropriate.

Conclusion

Women with EM have unmet information needs and are supportive of a comprehensive QPL including a wide range of topics related to EM. The recently developed EM QPL was perceived to be acceptable and feasible by women and relevant HPs.

This QPL was a part of a translational program to co-design evidence based online resources for women with EM aiming to improve knowledge and communication, facilitate health care and improve outcomes.

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Figure Legends

Figure 1. The process of developing the early menopause (EM) question prompt list (QPL):

- A survey of women with EM and feedback from expert reviewers informed the content of the EM QPL version 1
- Participants' feedback in two rounds interviews and the subsequent refinements contributed to development of QPL version 2 and 3.
- EM QPL version 3 was pilot-tested in a specialist menopause outpatient clinic

Note: HPs, health professionals; GP, general practitioners

Figure 2. Women's responses from Phase 1 survey (n=263) regarding communication with health professionals and topics to include in a question prompt list.

2A) Aspects of early menopause that women found difficult to talk with health professionals

2B) Topics identified by women as essential or very important, somewhat important and not important to include in an early menopause question prompt list. Topics are listed in descending order of importance.

Note: EM, Early menopause; CAM, Complementary and alternative medicines; MHT, Menopausal hormone therapy; QoL, Quality of life

Supplemental Digital Content

1. Early Menopause QPL Survey (word document)
2. Early Menopause QPL Interview Guide (word document)
3. Early Menopause QPL Survey for Pilot Study: Women (word document)
4. Early Menopause QPL Pilot Study: Clinician Feedback (word document)
5. Supplemental Table 1: Associations between survey participant characteristics and likelihood of using an early menopause QPL, determined using univariate/multivariate logistic regression analysis (word document)
6. Supplemental Table 2: Early menopause question prompt list modifications based on women's suggestions during two rounds of interviews (word document)

Chapter 5: Conclusions and future directions

EM/POI is associated with numerous physical and psychological risks including menopausal symptoms, impaired QoL, cognitive impairment, CVD, osteoporosis, mood disorders, sexual dysfunction, and premature death (43). Early diagnosis and management of EM/POI offers opportunities to relieve symptoms, improve QoL and prevent the long-term health implications (25). However, my thesis outlines that there are knowledge gaps regarding women's information needs, lifestyle management in GC survivors and the optimal diagnostic criteria, monitoring and management for EM/POI including hormone therapy regimen, which may result in delayed diagnosis, suboptimal care, variation in management, non-adherence with treatment, and poor outcomes (2, 57, 81). There is also a lack of high quality guidelines and a lack of implementation plan. Together these highlight the need to increase evidence-based understanding of EM/POI, to improve diagnosis/management and enhance women and HPs interactions leading to improved patient empowerment and health care.

MHT was widely advocated as a therapeutic standard for menopause until 2002 when the publication of the WHI study indicated that the risks of combined MHT may outweigh the benefits over an average 5 years of follow-up in women aged over 50 years (58). Although, there is no evidence indicating direct applicability to women with EM, these results led to significant uncertainties among clinicians (114) and impacted prescribing practices for women with EM with fewer prescriptions and decreased use of MHT (115). However, the re-analysis of WHI results demonstrated no significant increase in breast cancer, CVD and mortality risks following MHT use in women under 60 years (61, 116). Since then, several studies indicated significant changes in HPs' attitudes and prescribing habits concerning menopause management (57, 117). Differences were also found between specialties regarding diagnosis and management of EM in women with breast cancer (57). The applicability of the WHI findings to women with EM/POI is unclear and recent evidence and guidelines strongly support the use of MHT in this population, if there is no contraindication, until the age of natural menopause (6, 118).

The conflicting evidence and inconsistencies regarding menopause management, led to my study to assess the knowledge and attitudes of Australian HPs (GPs, endocrinologists and gynaecologists) regarding menopause management including EM/POI. The results of this study indicate significant knowledge gaps and discrepancies among HPs by field of practice in terms of MHT indications and duration of use. Women with EM/POI require estrogen replacement at least until the average age of natural menopause which can include both MHT and combined oral contraceptive pills (OCPs) (6, 119). In our survey, HPs reported that vasomotor symptoms (as opposed to disease prevention) was the main indication for

oestrogen therapy in women with EM/POI. OCPs were reported as the preferred systemic therapy for women with EM/POI and would be recommended by most HPs until the average age of natural menopause. However, variation was observed between specialties regarding duration of therapy; a greater proportion of endocrinologists advised a longer duration. In contrast, transdermal MHT was recommended by most HPs, as the first-line therapy for symptomatic menopause women aged over 50 years.

However, our systematic review and appraisal of menopause guidelines suggest that MHT would be preferable to the OCP, for women with EM/POI. Consistent with published evidence/guidelines (12, 116, 119, 120), most HPs in our study were reluctant to recommend MHT for chronic disease prevention in postmenopausal women. However, MHT is advocated for women with EM/POI for this purpose (6), reflecting another area of confusion for HPs related to EM/POI. Similar to previous research (117), HPs perceived women's concern regarding breast cancer risk as the major barrier to prescribing MHT. The reported knowledge and practice inconsistent with guidelines highlights the need for accessible educational resources addressing various menopause-related topics.

The lack of high quality guidelines may be a significant contributor to HPs knowledge gaps. CPGs are important tools which assist HPs in clinical decision making (91). Guidelines can be used to reduce inappropriate variations in practice and facilitate the implementation of high quality, evidence-based health care (92). However, despite an increasing number of CPGs over the last decades, poor methodological and content quality are still barriers to effective implementation of guidelines in clinical practice (93, 94). There are numerous published menopause CPGs with unclear methodological quality. Here, I led the first assessment of the quality of menopause CPGs using a validated tool (AGREE II), and reported significant deficiencies in the current menopause CPGs, with only two guidelines assessed as high quality. These high quality guidelines were used to develop an EM/POI management algorithm for HPs.

Consistent with the previous reviews (121, 122), CPGs achieved high score (over 70%) in two AGREE II domains, "scope and purpose" and "clarity of presentation". However, the clinical applicability of menopause guidelines is low, which potentially limits clinical use. Overall, menopause CPGs lack an implementation plan, limiting uptake in the clinical setting and local relevance. Menopause CPGs also varied in terms of the content and recommendations. High quality guidelines (NICE (119), ESHRE (6) and IMS (12)) differed in terms of diagnostic criteria for POI and some aspects of management. General menopause guidelines lacked comprehensive EM/POI information and recommendations were generally based on expert opinions and low level of evidence, reflecting the lack of high quality RCTs. The knowledge

gaps that I have identified were CPGs deficiencies in some domains such as applicability and stakeholder involvement, variation in criteria for EM/POI diagnosis and management including hormone therapy regimen and OCP administration and lack of high quality evidence, where more research is required. This study also highlighted the critical need for locally based implementation strategies.

Premenopausal women with GC develop EM/POI following cancer treatment. Observational studies indicated that EM is associated with higher risk of CVD and overall mortality (42, 123) and confirm the importance of lifestyle modifications on prevention of chronic disease in post-menopausal women (124). Previous non-randomized trials on GC survivors have reported inconsistent results on the beneficial effects of lifestyle interventions on QoL (125, 126). My comprehensive systematic review and meta-analysis of RCTs comparing lifestyle intervention (diet, exercise, behavioural interventions) with control (usual care or other lifestyle interventions) in GC survivors revealed significant methodological limitations with only a small number of eligible studies. Although the results of this study showed that the lifestyle modification did not improve individual QoL domains in women with GC, we cannot make conclusion based on two studies. This review underlines the paucity of evidence around lifestyle factors and cancer recurrence/survival and QoL in GC survivors. Well-designed, larger and longer term RCTs are required to determine whether healthy behaviours may have potential effects on disease free and QoL in women who have survived endometrial or ovarian cancer.

The specific needs of women experiencing EM/POI have not been well identified. To address this gap, I performed a survey to explore women's information needs and perspectives regarding online health resources. Sexual and psychological issues are common among women with EM/POI and may have significant impact on QoL (127), however, health care providers are often unable to appropriately address or manage these issues (128). Women in our study felt it was difficult to communicate with HPs about their sexual and psychological concerns and supported the concept of a communication tool such as a QPL including a full range of EM/POI-related topics. Evidence-based online resources such as a QPL can promote education and improve shared decision-making (108), with QPLs developed in various medical settings to facilitate question asking and improve health outcomes (107, 108).

This led to me co-designing a novel EM QPL with consumer input. Women perceived the QPL as a comprehensive, highly relevant and user-friendly resource, which may prompt them to ask questions in areas they had never considered. I also showed that women's information needs varied depending on the cause of EM/POI and the time since diagnosis. In line with

previous oncology studies (72, 108, 129), our findings indicated that an EM QPL would assist women to meet communication and information needs and facilitate information seeking. Women's input was incorporated and the QPL adapted iteratively with the final version then undergoing pilot testing in a hospital specialist menopause clinic. Feedback from this testing indicated that women and HPs generally perceived the QPL as an effective communication tool which facilitated question asking and/or raising concerns. Most women did not report anxiety with using the QPL during consultations. Women suggested they preferred to receive the QPL in the early stage of diagnosis and treatment. Most HPs did not express any concern that the QPL may extend the consultation length.

The findings of this pilot-study suggest that the EM QPL is an acceptable and feasible resource for stakeholders in a specialist outpatient clinic setting. Additional research is needed to identify the specific information needs and perspectives of women with different sociodemographic, cultural, or linguistic backgrounds as well as diverse EM/POI experiences. Potential barriers to effective implementation of the EM QPL includes the impact on the time and flow of the consultation which may vary between practice type (eg GP versus specialist) and needs to be formally assessed in future research. Suggestions to overcome the time dependent limitations of incorporating the QPL into a busy practice was the written suggestion in the early pages of the QPL, for women to (i) view the provided EM websites prior to their appointment to find answers to some of their questions and (ii) limit their questions to 1-3 at each appointment. Making a longer consultation time, involvement of a nurse practitioner to provide education may also assist with time dependent issues. To facilitate implementation of the QPL, further research is required to identify barriers and enablers in the various practice types and also with women from different backgrounds, varying literacy levels and non-English speakers. Upskilling of health professionals may also be required to enable them to provide the requested information.

My studies have informed the development of a website resources related to EM/POI for consumers and HPs. EM/POI websites may be helpful with HP and consumer education, improved patient experience, promotion of best practice and optimal health outcomes. This comprehensive website comprises: (i) Consumer and HPs experiences illustrated by audio / text clips (conducted with collaborators at RMIT); (ii) QPL to facilitate discussion and partnership in care with HPs; (iii) Other prioritized resources such as fact sheets with topics as determined by stakeholders (conducted by our research collaborators); (iv) Management algorithm for HPs which we developed from the CPG appraisal and (v) Resources page with links to relevant websites. Further evaluation of the EM website and translation into other

settings such as a mobile app may increase the effectiveness and user-friendliness of the website.

We are currently conducting user assessment of the web site assessing women's and HPs' satisfaction, knowledge change and health related behaviour. In my post-doctoral studies, I plan to complete this work before launching the web site in late 2019.

In summary, the research presented in this thesis has identified women's information and communication needs and HPs' knowledge gaps regarding EM/POI and treatment options. The paucity of high-quality evidence on treating EM/POI, confusion regarding available evidence, significant shortcomings in the available CPGs including lack of implementation strategies, consumer misconceptions and communication difficulties contribute to suboptimal care of women with EM/POI. These findings emphasize the need for further research to underpin the evidence base supporting rigorously developed guidelines and HP management resources with a strategy for implementation. Facilitation of consumer-HP communication and addressing women's education needs, via techniques such as the newly developed EM QPL, are promising but further implementation research is required. By increasing evidence-based understanding of EM/POI, this research can contribute to improved and earlier diagnosis of women with EM/POI, decreased variation in care and enhance women and HPs interactions potentially leading to patient empowerment and improved health care and outcomes for women with EM/POI. Providing resources in both website and app format would meet women's preferences and needs. Overall, the work presented advances knowledge in the field of EM/POI and illustrates a potential model for addressing HP and consumer knowledge gaps for other health conditions areas, thus providing a basis for future research.

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Appendices:

Appendix 1:

1.1 EM Consumer information survey

1.2 QPL

1.3 Poster (Developing an EM QPL)

1.4 Poster (Women's perceptions regarding EM e-health resources)

Appendix 2: HPs survey (attitudes to HRT prescribing practices)

Evidence of additional publications produced during candidature

Appendix 3: Complementary and Alternative Medicine (CAM) use in women with Primary Ovarian Insufficiency.

Kulkarni M, **Yeganeh L**, Vollenhoven B, Vincent AJ. Complementary and Alternative Medicine (CAM) use in women with Primary Ovarian Insufficiency. *Submitted to "Complementary Therapies in Medicine"*.

Appendix 4: Premature Ovarian Insufficiency/Osteoporosis clinical practice guideline systematic review.

Kiriakova V, Cooray SD, **Yeganeh L**, Somarajah G, Milat F, Vincent AJ. Management of bone health in women with premature ovarian insufficiency: Systematic appraisal of clinical practice guidelines and algorithm development. *Maturitas*. 2019, 128: 70-80.

Early menopause consumer information survey

Early menopause affects up to 10% of women. The Monash Centre for Health Research and Implementation at Monash University would appreciate your help in finding out what electronic resources women usually use to manage their health and what women would want in an early menopause resource. The findings of this research will help with the development of such a resource.

This survey is for women who have been diagnosed with early menopause (menopause before 45 years) or premature menopause / premature ovarian insufficiency (POI) (menopause before 40 years) by their doctor, live in Australia and are aged 20 years or more.

It should take approximately 15 minutes to complete and is anonymous with no personal details collected. You do not have to answer any question you are not comfortable with, and you may stop participating at any point. By taking this survey you consent the use of anonymous information to inform and improve education and care in early menopause. If you have any questions about this research please feel free to contact Ladan Yeganeh by email: MCHRI-earlymenopausestudy@monash.edu

This research has been approved by the Monash Health Human Research Ethics Committee. If you would like to make a complaint, you may contact:

Ms Deborah Dell (HREC Manager)

Phone: 03 95944605

Email: deborah.dell@monashhealth.org

In this survey, all women with premature menopause and premature ovarian insufficiency are also considered as early menopause.

-
1. Have you been diagnosed with early menopause (EM), premature menopause (PM) or premature ovarian insufficiency (POI) by a medical doctor?

☐ I have received a medical diagnosis of EM, PM or POI

☐ I think I have EM, PM or POI but I haven't received a formal diagnosis yet

☐ I don't know which one of these I have been diagnosed, but I have been diagnosed with menopause earlier than usual

☐ I don't know if I have been diagnosed with any of these

-
2. What is your current age?

-
3. Were you born in Australia?

☐ Yes

☐ No

If no, which country were you born in:

-
4. What state or territory do you live in?

☐ Victoria

☐ New South Wales

☐ Queensland

☐ South Australia

☐ Western Australia

☐ Tasmania

☐ Northern Territory

☐ Australian Capital Territory

☐ I do not live in Australia

-
5. How would you describe where you live?

☐ Metropolitan (i.e. city location)

☐ Regional location

☐ Rural location

☐ Remote location

-
6. How many years have you lived in Australia?

☐ Less than 1 year

☐ 1-4 years

☐ 5-9 years

☐ 10 years or more

-
7. What is the highest level of education you have completed?

- ☐ Less than Year 12 or equivalent
 - ☐ Year 12 or equivalent
 - ☐ Vocational qualification (e.g. apprenticeship)
 - ☐ Associate Diploma
 - ☐ Undergraduate Diploma
 - ☐ Bachelor degree (including honours)
 - ☐ Postgraduate diploma
 - ☐ Master's Degree
 - ☐ Doctorate (PhD)
-

8. Are you of Aboriginal or Torres Strait Islander descent?

- ☐ Yes, I am Aboriginal
 - ☐ Yes, I am Torres Strait Islander
 - ☐ Yes, I am both Aboriginal and Torres Strait Islander
 - ☐ No, I am neither
-

9. How long ago were you diagnosed with early menopause?
- ☐ Less than 1 year ago
 - ☐ 1-2 years ago
 - ☐ 3-4 years ago
 - ☐ 5 or more years ago
 - ☐ I haven't received a diagnosis of early menopause from a doctor yet
-

10. What age were you diagnosed with early menopause?
-

11. When was your last menstrual period?
- ☐ More than 12 months ago
 - ☐ 6-12 months ago
 - ☐ 3-6 months ago
 - ☐ < 3 months ago
-

12. What is the cause of your early menopause?
- ☐ Genetic (e.g. Turner syndrome, Fragile x)
 - ☐ Autoimmune disorders
 - ☐ Cancer treatment
 - ☐ Surgical removal of ovaries
 - ☐ Metabolic disorders
 - ☐ No known cause
 - ☐ Other (please specify)
-

13. Have you been diagnosed with cancer?
- ☐ Yes
 - ☐ No

If yes, please specify the type of cancer:

14. Have you had any of the following treatments? (Select all that apply)
- ☐ Chemotherapy
 - ☐ Radiotherapy
 - ☐ Surgical removal of both ovaries
 - ☐ Hysterectomy with no removal of the ovaries
 - ☐ Hysterectomy and surgical removal of both ovaries
 - ☐ I have not had any of these treatments
-

15. Which electronic devices do you own or have access to? (Select all that apply)

- ☐ Mobile phone but not a smartphone
- ☐ iOS smartphone (iPhone)
- ☐ Android smartphone (e.g. Samsung)
- ☐ Laptop
- ☐ Tablet/iPad
- ☐ Desktop Computer
- ☐ None
- ☐ Other (please specify)

16. Have you ever used an electronic device to help manage aspects of early menopause?

- ☐ Yes ☐ No

17. Which electronic devices, if any, have you used to manage your health in the past (e.g. find health-related information, monitor symptoms, track changes, find a health professional)? (Select all that apply)

- ☐ Mobile phone but not a smartphone
- ☐ iOS smartphone (iPhone)
- ☐ Android smartphone
- ☐ Laptop
- ☐ Tablet/iPad
- ☐ Desktop Computer
- ☐ Electronic wearable fitness device (e.g. fitbit, jawbone etc.)
- ☐ None
- ☐ Other (please specify)

18. If yes, how often do you use electronic devices for each of the following tasks?

	Never	A few times a year	Once a month	Once a week	Once a day
Finding menopause-related information	m	m	m	m	m
Setting health-related goals	m	m	m	m	m
Tracking menopausal symptoms	m	m	m	m	m
Tracking your weight	m	m	m	m	m
Monitoring your mood	m	m	m	m	m
Send health reminders (e.g. reminders to exercise, reminders to attend medical appointments, medication reminders)	m	m	m	m	m
Getting social support (e.g. looking at menopause forums, finding support groups)	m	m	m	m	m
Find a health professional	m	m	m	m	m
Monitoring medications	m	m	m	m	m
Tracking menstrual cycles in past	m	m	m	m	m

19. Are there any other health tasks you use electronic devices for? (Please specify)

20. Overall, which electronic resource would you be more likely to use to help manage early menopause?

☐ Website

☐ Mobile application (app)

21. Have you ever used an app before to manage your health? (Select all that apply)

☐ Yes, to manage an aspect of early menopause

☐ Yes, to manage my general health

☐ Yes, to manage another health condition unrelated to menopause

☐ No

☐ If yes, please specify which app

22. If no, is there a reason why this is so? (Select all that apply)

☐ There is no reason in particular

☐ I did not want to pay for an app

☐ I could not find an app that met my healthcare needs

☐ I do not have access to a smartphone/tablet

☐ I don't think healthcare apps are useful

☐ Other (please specify)

23. Please rate your opinion and agreement with the following statements about apps (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree)

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Healthcare apps, when used properly, improve people's health	m	m	m	m	m
Healthcare apps make it easier to eat a healthy diet	m	m	m	m	m
Healthcare apps make it easier to maintain an exercise plan	m	m	m	m	m
Healthcare apps are more effective than websites at improving people's health	m	m	m	m	m
Healthcare apps are best when they provide accurate health information	m	m	m	m	m
Healthcare apps are best when they are interactive	m	m	m	m	m
Healthcare apps are best when they connect to my other social media accounts (e.g. Facebook, Twitter)	m	m	m	m	m
Healthcare apps are best when they allow me to interact with other members of the app community	m	m	m	m	m
Healthcare apps are best when they are light-hearted and fun	m	m	m	m	m
Healthcare apps are best when they link to other healthcare apps and health websites	m	m	m	m	m
Healthcare apps are best when they don't require me to access the internet during use	m	m	m	m	m
A healthcare app specifically for women with menopause would help women to manage menopause more effectively	m	m	m	m	m
I would use a					

healthcare app
specifically for
menopause

m

m

m

m

m

24. What features do you think are important to include in an app specifically designed to help women manage their early menopause?

	Not important at all	Not very important	Somewhat important	Very important	Essential
Provides me with current, up-to-date information on early menopause that has been validated by health professionals (i.e. evidence-based information)	m	m	m	m	m
Allows me to record my symptoms and other health measures (e.g. weight, blood pressure, mood, hot flushes)	m	m	m	m	m
Sends me notifications (e.g. health check reminders, encouragements to exercise)	m	m	m	m	m
Rewards me for positive health behaviour (e.g. with encouragement, leader boards)	m	m	m	m	m
Allows me to set my own health-related goals	m	m	m	m	m
Allows me to share my progress with my friends or other members of the app community	m	m	m	m	m
Allows me to connect and interact with other women with early menopause	m	m	m	m	m
Opportunities to ask an expert about certain aspects of menopause (e.g. gynaecologists, endocrinologists)	m	m	m	m	m
A list of questions that I can ask my healthcare professional at my appointments (a Question Prompt List)	m	m	m	m	m
Manage/check medication	m	m	m	m	m
Health appointment reminders	m	m	m	m	m

25. What other features do you think are important to include in an app?

One feature that an app or website can include is a Question Prompt List. Question Prompt Lists are lists of questions on a particular medical condition that people can take to their appointments and refer to during the consultation. The questions are grouped according to subjects so that people can easily identify which questions they would like to ask. These are created so that people interact with their healthcare provider as much as possible, to get the most out of their consultation and to work in partnership to manage their health.

26. What aspects of early menopause do you currently find difficult to talk to health professionals about? (Select all that apply)

- ☐ What causes early menopause
- ☐ What is early menopause
- ☐ How is early menopause diagnosed
- ☐ Physical effects of early menopause
- ☐ Hot flushes / night sweats
- ☐ Vaginal or urinary symptoms
- ☐ Other menopausal symptoms
- ☐ Psychological effects (depression, anxiety, mood change)
- ☐ Long term consequences such as bone loss, heart disease
- ☐ Bone health
- ☐ Heart and cardiovascular health
- ☐ Sexual function
- ☐ Hormonal treatments (HRT)
- ☐ Non-hormonal treatments
- ☐ Complementary & alternative therapies
- ☐ Lifestyle changes
- ☐ Infertility
- ☐ Other (please specify)

27. How helpful do you think a Question Prompt List for early menopause be to assist you to communicate with your healthcare provider during a consultation?

- ☐ Not at all
- ☐ A little
- ☐ Somewhat
- ☐ Very
- ☐ Extremely

28. Would you be likely to use a Question Prompt List during consultations with your healthcare provider, if it was easily available?

- ☐ Not at all likely
- ☐ Unlikely
- ☐ Neutral
- ☐ Likely
- ☐ Very likely

29. If not at all likely or unlikely, is there a particular reason why? (Select all that apply)

- ☐ I find it very easy to communicate with health professionals about early menopause already
- ☐ I don't understand how a Question Prompt List would work
- ☐ I don't think my health professional would be supportive of me using a Question Prompt List
- ☐ Other (please specify)

30. What do you consider useful to include in a website for women with early menopause? (Select all that apply)

- ☐ Question Prompt List
- ☐ Information sheet that can be printed off
- ☐ Video clips regarding the experiences of women with early menopause
- ☐ Links to other relevant websites
- ☐ Support groups / find a doctor
- ☐ Information about early menopause
- ☐ Social media links (e.g. facebook / twitter)
- ☐ Information about early menopause that can be read online
- ☐ Other (please specify)

31. Which information about early menopause is important to include in a website, Question Prompt List, fact sheet or App? (Select all that apply)

	Not important at all	Not very important	Somewhat important	Very important	Essential
What is early menopause	m	m	m	m	m
What are the causes of early menopause	m	m	m	m	m
How is early menopause diagnosed	m	m	m	m	m
Physical effects of early menopause	m	m	m	m	m
Hot flushes / night sweats	m	m	m	m	m
Vaginal or urinary symptoms	m	m	m	m	m
Other menopausal symptoms	m	m	m	m	m
Psychological effects (eg. depression, anxiety, mood change)	m	m	m	m	m
Long-term effects of early menopause	m	m	m	m	m
Bone health	m	m	m	m	m
Heart and cardiovascular health	m	m	m	m	m
Sexual functions	m	m	m	m	m
How early menopause affects quality of life	m	m	m	m	m
How to relieve menopausal symptoms	m	m	m	m	m
Hormonal treatments (HRT)	m	m	m	m	m
Types of HRT	m	m	m	m	m
Duration of HRT	m	m	m	m	m
Effectiveness of treatment for symptoms	m	m	m	m	m
Hormone therapy risks	m	m	m	m	m
Hormone therapy benefits	m	m	m	m	m
Possible interactions of hormone therapy with other medications	m	m	m	m	m
Any tests before starting the treatment	m	m	m	m	m
Non-Hormonal treatments for menopausal	m	m	m	m	m

symptoms					
Types of non-hormonal treatments	m	m	m	m	m
Duration of non-hormonal therapy	m	m	m	m	m
Effectiveness of non-hormonal treatments for symptoms	m	m	m	m	m
Non-hormonal therapy risks	m	m	m	m	m
Possible interactions of non-hormonal therapy with other medications	m	m	m	m	m
Any tests before starting non-hormone therapies	m	m	m	m	m
Complementary & Alternative therapies	m	m	m	m	m
Lifestyle changes	m	m	m	m	m
Infertility	m	m	m	m	m
Others (please specify)	m	m	m	m	m

32. Please specify what other information you would like to include?

33. What words do you associate with early menopause?



Early Menopause

QUESTION PROMPT LIST

This question prompt list (QPL) is for women with early menopause (EM) and premature ovarian insufficiency (POI). These are all questions that are OK to ask your doctor or health professional. You may have been diagnosed recently or a long time ago. It is for women of all ages and backgrounds.

You can use this QPL to ask a few questions that are important to you now. You don't have to ask the questions exactly the way they are written here, you can adapt them. Some of the questions may not apply to you as EM affects different women in different ways.

How do I use the QPL?

1. **Part 1** contains the list of questions and **Part 2** contains links to further information. The following websites have information about EM/POI and also hints about finding information on the internet. In Part 2 there are other websites listed with each topic which can be helpful but may not be specific to EM/POI. We suggest you look at one or more of these sites first. Then think about the questions that are most important to you right now. Also, if you read something on the internet that you don't understand then you can ask your doctor about it.

General early menopause information

Australian websites:

www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/premature-and-early-menopause

www.jeanhailes.org.au/health-a-z/menopause/premature-early-menopause

International websites:

www.nhs.uk/conditions/early-menopause

www.hormone.org/menopausemap/premature_menopause.html

www.patient.info/health/menopause-hrt/premature-ovarian-insufficiency

www.menopause.org/for-women/expert-answers-to-frequently-asked-questions-about-menopause/perimenopause-premature-menopause-faqs

www.hormone.org/diseases-and-conditions/womens-health/primary-ovarian-insufficiency

www.mayoclinic.org/diseases-conditions/premature-ovarian-failure/symptoms-causes/syc-20354683

Spontaneous POI

www.menopause.org.au/hp/information-sheets/742-spontaneous-premature-ovarian-insufficiency

www.eshre.eu/~media/sitecore-files/Guidelines/POI/ESHRE-POI-GUIDELINE_Patient-version_noniatrogenic-POI.pdf

Medically-induced POI

www.menopause.org.au/hp/information-sheets/319-early-menopause-due-to-chemotherapy-radiotherapy

www.eshre.eu/~media/sitecore-files/Guidelines/POI/ESHRE-POI-GUIDELINE_Patient-version_iatrogenic-POI.pdf

www.bcna.org.au/media/5850/hormone-therapy-and-breast-cancer-booklet-112017.pdf

www.canceraustralia.gov.au/sites/default/files/publications/bcmc-breast-cancer-early-menopause-v2_504af03adb71c.pdf

Using the Internet to Research Menopause Health Information

<https://beta.healthtalkaustralia.org/wp-content/uploads/2018/10/Fact-Sheet-Using-the-internet-to-research-menopause-related-information.pdf>

Early Menopause: Women's Experiences

<https://beta.healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/overview-womens-experiences/>

2. There still needs to be time for your doctor or health professional to do any physical checks, ask questions also, and talk with you about the management plan that's best for you. So even if you have lots of questions, try 1-3 to start with. Talk with your doctor about other options for having your questions answered. Sometimes you can book a longer appointment or you can see someone else at the clinic like the practice nurse. Your doctor might give you a referral to a different type of health professional depending on your questions
3. Keep your QPL with your other health documents. Look at it before any EM/POI related appointment. Different questions might be important to you at different times, so mark the tick boxes relevant to you so you can use the QPL again and again. You might want to give a copy of your QPL to your health professional to keep in your record too.
4. The following links provide a glossary of terms related to menopause that may be helpful
www.menopause.org.au/hp/information-sheets/381-glossary-of-terms
www.menopause.org/for-women/menopause-glossary

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PART 1 – QUESTION PROMPT LIST

Causes, diagnosis, symptoms

What is early menopause?

- ☐ How does EM differ from natural menopause?
- ☐ What are the differences between premature ovarian insufficiency (POI), premature ovarian failure, premature menopause and early menopause?
- ☐ How common are EM and POI?
- ☐ Can EM/POI be prevented?

Causes of early menopause

- ☐ What are the causes of EM/POI?
- ☐ Is EM/POI an inherited disease (run in families)?
- ☐ Will my daughter(s) also develop EM/POI?
- ☐ Should my daughter be told to have children early?
- ☐ Are genetic tests needed in women with EM/POI?
- ☐ What increases my risk of EM/POI?
- ☐ What is medically induced EM/POI?
- ☐ What is spontaneous EM/POI?

Diagnosis

- ☐ How is EM/POI diagnosed?
- ☐ I have irregular periods. Do I have EM/POI?
- ☐ What tests do I need to have to diagnose EM/POI?
- ☐ How many times do I need to do the tests for diagnosis?
- ☐ What do my test results mean?
- ☐ What tests do I need to do to find the cause of EM/POI?

Symptoms

- ☐ What are the symptoms of EM/POI?
- ☐ Do all women with EM/POI experience symptoms?

- ☐ Are menopause symptoms more severe in EM/POI compared with menopause at a usual age (about 50 years)?
- ☐ What are hot flushes?
- ☐ How long will I have hot flushes?
- ☐ I have difficulty sleeping. Is it a sign of EM/POI?
- ☐ What body changes are associated with EM/POI?
- ☐ Does EM/POI cause hair and skin changes?
- ☐ Does EM/POI cause changes in urinary or vaginal symptoms?
- ☐ Does EM/POI cause changes in sexual function?
- ☐ Does EM/POI cause mood changes?
- ☐ Are there any special symptoms or signs associated with different causes of EM/POI?
- ☐ Can my menstrual period come back after they have stopped?

Sexual, urinary and vaginal health

Sexual, urinary and vaginal symptoms:

- ☐ What are the effects of EM/POI on sexuality and urinary/vaginal function?

Treatments for sexual, urinary and vaginal symptoms:

- ☐ What is the best treatment for vaginal pain, dryness and discomfort?
- ☐ Can lubricants and moisturizers help vaginal discomforts?
- ☐ What can I do if sex is painful?
- ☐ Can I use more than one treatment?
- ☐ Can I have vaginal oestrogen treatment (creams or tablets) in addition to other forms of HRT?
- ☐ Does vaginal estrogen treatment (creams or tablets) work as well as other types of HRT?
- ☐ Are the side-effects of different hormonal treatments, vaginal, oral or transdermal (through the skin e.g. patches or gel) the same?
- ☐ I have heard about laser therapy for vaginal symptoms. What is it and how does it work?
- ☐ How can I improve my sexual relationship?
- ☐ What is testosterone therapy for sexual function problems?

Psychological effects of early menopause

- ☐ Does EM/POI have effects on mood (anxiety, depression)?

- ☐ How do I know if I have anxiety or depression?
- ☐ I feel tired and have stress most of the time. Is it related to EM?
- ☐ How I can improve my self-esteem?
- ☐ What are the best treatment options for depression and anxiety?
- ☐ Do I need to see a psychologist?
- ☐ Can EM affect my relationship?
- ☐ What are the psychological effects of infertility associated with EM/POI?

Fertility

- ☐ Does EM/POI make it more difficult to get pregnant?
- ☐ Is there any chance of pregnancy (without medical help)?
- ☐ Do women with EM/POI need to use contraception if they do not want to get pregnant?
- ☐ How is infertility treated in EM/POI?
- ☐ What is the best treatment option for fertility?
- ☐ Can I use assisted reproductive techniques?
- ☐ How long should I try to become pregnant before seeing a fertility doctor?
- ☐ Do I need to try to become pregnant now or I can wait until I become ready?
- ☐ Should I consider freezing my eggs, or is too late?
- ☐ How would I know if I am pregnant when taking HRT?
- ☐ What are the psychological effects of infertility associated with EM/POI?

Long term effects of early menopause

- ☐ What are the long-term effects of EM/POI on my health?
- ☐ Are EM/POI effects more severe than menopause at the usual age (about 50 years)?

Brain health

- ☐ I have difficulty concentrating. Is it related to EM/POI?
- ☐ I have memory problems. Is it related to EM/POI?
- ☐ What can I do to improve my brain health?
- ☐ Do women with EM have an increased risk of Alzheimer's disease?

- ☐ Can HRT decrease my risk of Alzheimer's disease?

Bone health

- ☐ Are women with EM/POI at risk of bone loss?
- ☐ How common is bone loss in EM/POI?
- ☐ What are the risk factors for bone loss in women with EM/POI?
- ☐ Does family history change my risk of bone loss?
- ☐ Can any medications cause bone loss?
- ☐ What are the symptoms of bone loss?
- ☐ Are there any tests to check for bone loss and how often should I have tests?
- ☐ Is there an increased risk of bone fracture (breaking of bone) later in life?

Prevention and treatment of bone loss

- ☐ How can I prevent bone loss (decreased bone density/osteoporosis)?
- ☐ What is the best treatment for bone loss?
- ☐ Does a healthy lifestyle improve bone health?
- ☐ What is the best diet for preventing bone loss?
- ☐ What are the best sources of calcium and vitamin D?
- ☐ How much calcium do I need to have in my diet?
- ☐ Do I need to use any supplements (calcium, vitamin D) to prevent/treat bone loss and are they safe?
- ☐ Is it safe to use dietary supplements?
- ☐ Do I need to be more active or exercise more to prevent/treat bone loss?
- ☐ Is there any specific exercise for bone protection?
- ☐ What exercises or activities should I avoid?
- ☐ Which health professional should I see for more support about physical activity or exercise?

Heart and metabolic health

- ☐ Do women gain weight after menopause?
- ☐ Are women with EM/POI at higher risk of heart disease/stroke?
- ☐ How do I check my risk of heart disease/stroke?
- ☐ How can I reduce my risk of heart disease/stroke?

- ☐ What lifestyle changes help reduce my risk of heart disease/stroke?
- ☐ What medications reduce my risk of heart disease/stroke?

Breast health

- ☐ I have breast cancer- What are my EM treatment options?
- ☐ Does EM/POI affect my risk of breast cancer?
- ☐ What if I take HRT - how does that effect my breast cancer risk?
- ☐ I have family history of breast cancer. Can I take HRT?

Treatment of early menopause

- ☐ What are the treatments for EM/POI?
- ☐ Do I need treatment if I do not have any symptoms?
- ☐ What is the aim of the treatment?
- ☐ Do symptoms get better without any treatment?

Hormonal Replacement Therapy (HRT) or Menopausal Hormone Therapy (MHT)

Overview:

- ☐ What is HRT/ MHT?
- ☐ What do hormones do and why are they used for EM/POI?
- ☐ What are the different types of HRT?
- ☐ How effective is HRT?
- ☐ Is it necessary to have treatment right now or I can start later?
- ☐ Is HRT the best option for EM management?
- ☐ Can HRT be affected by other medicines?
- ☐ What are compounded bio-identical hormones and are they safe?
- ☐ Are there medical conditions where HRT is not safe for me?
- ☐ What is abnormal bleeding on HRT?
- ☐ Should I report unexpected/abnormal bleeding when taking HRT?
- ☐ What happens if I can't or don't want to take HRT?

Risks of HRT:

- ☐ What are the risks of HRT?

- ☐ Does HRT increase the risk of cancer in women with EM/POI?
- ☐ I have cancer. Is there any risk of cancer recurrence with HRT?
- ☐ Does HRT cause weight gain?
- ☐ I am overweight/obese. Can I use HRT?
- ☐ I have high blood pressure. Can I take HRT?
- ☐ Is HRT safe for women with a history of blood clots (venous thromboembolism)?
- ☐ Is HRT safe for women with a family history of blood clots (venous thromboembolism)?
- ☐ I get migraines. Can I take HRT?
- ☐ Who do I need to contact if any side-effects occur?
- ☐ How often should I have a check-up while taking HRT?
- ☐ What should I do if I can't take HRT?

Benefits of HRT:

- ☐ What are the benefits of HRT?
- ☐ Can HRT help to relieve hot flushes?
- ☐ How long should I use HRT for?
- ☐ Will hot flushes occur again if I stop treatment?
- ☐ Can HRT treat mood disorders and depression?
- ☐ Can HRT improve quality of life?
- ☐ Can HRT prevent bone loss and heart disease?

Non-hormonal treatments

- ☐ What are non-hormonal treatment options?
- ☐ What is the best non-hormonal treatment for reducing menopause symptoms?
- ☐ Are non-hormonal treatments as effective as hormonal medications?
- ☐ Are non-hormonal treatments effective and safe for women treated for breast or uterine cancer?
- ☐ Is there any over-the-counter non-hormonal treatment for EM/POI?

Lifestyle changes

- ☐ Is EM associated with weight gain?
- ☐ What is the ideal weight for me?
- ☐ Can a healthy diet prevent or treat signs of EM/POI?

- ☐ Is there one best diet for EM?
- ☐ Should I stop smoking?
- ☐ Do I need to reduce alcohol intake?
- ☐ Do I need to follow a regular exercise?
- ☐ Do I need to see a dietician?

Complementary medicine

- ☐ Do complementary therapies (such as traditional Chinese medicine, herbal medicine, acupuncture and lifestyle changes) help to relieve menopause symptoms?
- ☐ Can complementary treatments prevent bone loss and heart disease?
- ☐ Are complementary treatments safe?
- ☐ Are there over-the-counter products available for EM/POI?
- ☐ Should I see a complementary practitioner?

Support groups and where to seek help

- ☐ Is there an EM/POI support group?
- ☐ How can I get support from other people?
- ☐ How often should I see my doctor (GP, specialist)?
- ☐ How do I find a health professional that has a particular interest in EM/POI?

Additional questions

PART 2 – LINKS TO INFORMATION

Causes, diagnosis, symptoms

What is early menopause?

www.hormone.org/diseases-and-conditions/womens-health/primary-ovarian-insufficiency

Causes of early menopause

Spontaneous:

www.eshre.eu/-/media/sitecore-files/Guidelines/POI/ESHRE-POI-GUIDELINE_Patient-version_noniatrogenic-POI.pdf?

Medically induced:

www.eshre.eu/-/media/sitecore-files/Guidelines/POI/ESHRE-POI-GUIDELINE_Patient-version_iatrogenic-POI.pdf

www.menopause.org.au/hp/information-sheets/756-surgical-menopause

www.counterpart.org.au/podcasts/menopause-after-cancer/ (podcast)

www.jeanhailes.org.au/health-a-z/menopause/menopause-after-cancer

Diagnosis

www.hormone.org/diseases-and-conditions/womens-health/amenorrhea

www.eshre.eu/-/media/sitecore-files/Guidelines/POI/ESHRE-POI-GUIDELINE_Patient-version_noniatrogenic-POI.pdf?

Symptoms

www.menopause.org.au/health-info/menopause-videos/what-are-the-symptoms (video)

www.jeanhailes.org.au/health-a-z/menopause/menopause-symptoms

Hot flushes:

www.reproductivefacts.org/resources/infographic-gallery/images/anatomy-of-a-hot-flash

Difficulty sleeping:

www.menopause.org.au/hp/information-sheets/949-sleep-disturbance-and-the-menopause2

www.menopause.org.au/health-info/menopause-videos-for-women-from-nams/776-the-menopausal-transition-as-a-risk-factor-for-sleep-apnea-in-women (video)

Body changes:

www.menopause.org.au/hp/information-sheets/533-menopause-and-body-changes

www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/menopause-and-weight-gain

Hair/skin changes:

www.womens-health-concern.org/help-and-advice/factsheets/menopausal-hair-loss

Sexual, urinary and vaginal health

Sexual, urinary and vaginal symptoms:

www.menopause.org.au/hp/information-sheets/749-stress-and-urge-urinary-incontinence-in-women

www.menopause.org.au/hp/information-sheets/722-sexual-difficulties-in-the-menopause

www.jeanhailes.org.au/health-a-z/menopause/sex

www.breastcancer.org/treatment/side_effects/libido_loss

www.menopause.org/for-women/sexual-health-menopause-online

Treatments for sexual, urinary and vaginal symptoms:

www.jeanhailes.org.au/contents/documents/Resources/Booklets/The_vulva.pdf

www.menopause.org.au/hp/information-sheets/376-vulvovaginal-symptoms-after-menopause

www.menopause.org.au/hp/information-sheets/817-vaginal-health-after-breast-cancer-a-guide-for-patients

www.jeanhailes.org.au/health-a-z/menopause/menopause-management

www.menopause.org.au/health-info/menopause-videos-for-women-from-nams/816-vaginal-health (video)

www.menopause.org.au/health-info/menopause-videos/will-it-affect-my-sex-life (video)

www.menopause.org.au/health-info/menopause-videos-for-women-from-nams (video)

Psychological effects of early menopause

www.menopause.org.au/hp/information-sheets/570-mood-problems-at-menopause

www.jeanhailes.org.au/health-a-z/menopause/mental-health-emotions

www.menopause.org/for-women/menopauseflashes/mental-health-at-menopause/depression-menopause

www.menopause.org.au/health-info/menopause-videos-for-women-from-nams (video)

www.beyondblue.org.au

www.breast-cancer.canceraustralia.gov.au/living/emotional-changes

Fertility

<https://www.healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/resources-and-information-for-women/#a4>

www.canceraustralia.gov.au/sites/default/files/publications/bcmc-breast-cancer-early-menopause-v2_504af03adb71c.pdf

www.bcna.org.au/media/4448/bcn1189_fertility-cover2017-web.pdf
www.breast-cancer.canceraustralia.gov.au/living/physical-changes/fertility
[www.cancer.org.au/content/about_cancer/ebooks/livingwithcancer/Fertility and cancer booklet May 2016.pdf](http://www.cancer.org.au/content/about_cancer/ebooks/livingwithcancer/Fertility_and_cancer_booklet_May_2016.pdf)
www.reproductivefacts.org/resources/educational-videos/videos/full-length-videos/videos/fertility-preservation-for-cancer-patients (video)
www.reproductivefacts.org/faqs/faqs-about-the-psychological-component-of-infertility

Long term effects of early menopause

Brain health

www.breastcancer.org/research-news/20130801
www.menopause.org.au/health-info/menopause-videos-for-women-from-nams (video)

Bone health

[Premature Ovarian Insufficiency / Early Menopause and Osteoporosis infographic](#)
[Early Menopause / Premature Ovarian Insufficiency and Bone Health fact sheet](#)
www.menopause.org.au/health-info/self-assessment-tools/know-your-bones
www.bcna.org.au/news/2014/02/new-bone-health-and-breast-cancer-fact-sheet

Prevention and treatment of bone loss

www.menopause.org.au/hp/information-sheets/228-calcium-supplements-patient-guide
www.bcna.org.au/news/2014/02/new-bone-health-and-breast-cancer-fact-sheet
www.hormone.org/diseases-and-conditions/bone-health/vitamin-d-and-calcium
www.bcna.org.au/media/6468/exercise-and-breast-cancer-booklet-web.pdf
www.menopause.org/for-women/menopauseflashes/bone-health-and-heart-health/bone-health-exercise-is-a-key-component
www.osteoporosis.org.au/exercise

Heart and metabolic health

Weight gain:

www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/menopause-and-weight-gain
www.breastcancer.org/tips/menopausal/treat/weight-gain
www.mayoclinic.org/healthy-lifestyle/womens-health/in-depth/menopause-weight-gain/art-20046058

www.newsnetwork.mayoclinic.org/discussion/weight-gain-and-menopause-mayo-clinic-radio-health-minute (podcast)

Risk of heart disease/stroke:

www.menopause.org.au/health-info/self-assessment-tools/cardiovascular-disease

www.breastcancer.org/tips/menopausal/longterm_conc/heart

www.menopause.org/for-women/menopauseflashes/bone-health-and-heart-health/keeping-your-heart-healthy-at-menopause

www.menopause.org/for-women/menopauseflashes/exercise-and-diet

www.patient.info/health/menopause-hrt/features/your-diet-and-the-menopause

Breast health

www.canceraustralia.gov.au

www.bcna.org.au/media/5850/hormone-therapy-and-breast-cancer-booklet-112017.pdf

www.canceraustralia.gov.au/sites/default/files/publications/bcmc-breast-cancer-early-menopause-v2_504af03adb71c.pdf

www.menopause.org.au/hp/information-sheets/600-nonhormonal-treatments-for-menopausal-symptoms

www.petermac.org/iprevent

Treatment of early menopause

Hormonal Replacement Therapy (HRT) or Menopausal Hormone Therapy (MHT)

Overview:

www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/hormone-replacement-therapy-hrt-and-menopause

www.menopause.org.au/health-info/menopause-videos/what-is-menopausal-hormone-therapy-hrt

www.jeanhailes.org.au/health-a-z/menopause/menopause-management

www.menopause.org.au/hp/information-sheets/267-combined-menopausal-hormone-therapy-mht

www.menopause.org.au/hp/information-sheets/552-oestrogen-only-mht

www.menopause.org.au/hp/information-sheets/212-bioidentical-hormones-for-menopausal-symptoms

www.menopause.org.au/hp/information-sheets/1025-postmenopausal-bleeding-including-breakthrough-on-mht-hrt

Risks and benefits of HRT:

www.menopause.org.au/health-info/fact-sheets/what-is-menopausal-hormone-therapy-mht-and-is-it-safe

www.menopause.org.au/health-info/menopause-videos/is-menopausal-hormone-therapy-hrt-safe (video)

www.menopause.org.au/hp/information-sheets/799-risks-and-benefits-of-mht-hrt

www.womens-health-concern.org/help-and-advice/factsheets/hrt-know-benefits-risks

www.menopause.org.au/hp/information-sheets/524-venous-thrombosis-thromboembolism-risk

www.menopause.org.au/hp/information-sheets/560-migraine-headaches-menopause-and-mht-hrt

Non-hormonal treatments

www.menopause.org.au/health-info/menopause-videos/non-hormonal-treatment-options (video)

www.menopause.org.au/health-info/menopause-videos-for-women-from-nams/598-nonhormonal-therapy (video)

www.menopause.org.au/hp/information-sheets/600-nonhormonal-treatments-for-menopausal-symptoms

Lifestyle changes

www.jeanhailes.org.au/health-a-z/menopause/menopause-management

www.womens-health-concern.org/help-and-advice/healthy-menopause

www.breastcancer.org/tips/menopausal/treat/weight-gain

www.menopause.org/for-women/menopauseflashes/exercise-and-diet/drink-to-your-health-at-menopause-or-not

Complementary medicine

www.menopause.org.au/health-info/menopause-videos/complementary-therapies

www.menopause.org.au/hp/information-sheets/734-complementary-and-herbal-therapies-for-hot-flushes

www.womens-health-concern.org/help-and-advice/factsheets/cognitive-behaviour-therapy-cbt-menopausal-symptoms

www.womens-health-concern.org/help-and-advice/factsheets/complementaryalternative-therapies-menopausal-women

[www.menopause.org/docs/default-source/2013/what midlife women should know about hormone-therapy-alternatives.pdf](http://www.menopause.org/docs/default-source/2013/what%20midlife%20women%20should%20know%20about%20hormone-therapy-alternatives.pdf)

www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-treatments/natural-remedies-for-hot-flashes

Support groups and where to seek help

www.canceraustralia.gov.au/affected-cancer/cancer-support-organisations

www.bcna.org.au/media/3684/bcn1198_partnerbooklet-2016_online.pdf

Developing an early menopause question prompt list: women's information needs

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Background

Early menopause (EM) (menopause before 45 years) occurs spontaneously or secondary to medical treatment and affects up to 10% of women (1).

Women with early menopause report unmet information needs(2). A Question Prompt List (QPL) is a structured list of evidence-based questions which can assist women to obtain information relevant to their needs and facilitate communication between women and healthcare providers(3).

We aimed to explore perspectives and information needs of women with EM to inform the development of an EM QPL.

Methods

Study design

Participants

- Study was approved by Monash Health ethics.
- Women with self reported diagnosis of EM aged >20 years were recruited from hospital clinics or the community and invited to participate in an online or paper survey.

Tool

- Survey questions were adapted from a previous study involving the development of a polycystic ovary syndrome QPL(4) and studies of premature menopause (5,6).
- Data regarding demographics, medical history, perceptions regarding communication difficulties, QPL use and topics to include in a QPL were collected.

Exclusion criteria

- No EM diagnosis
- Non-Australian residence
- No English literacy

Statistical analysis

- Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0 was used for data analysis.
- Data analysis included descriptive statistics and logistic regression with P<0.05 considered significant.

Results

263/386 responses were suitable for analysis. Mean age of respondents was 53.81±10.67 and the majority (78%) were diagnosed with EM 5 or more years previously. Most participants were Australian born (81%), lived in metropolitan areas (55%) and had a post-school qualification (71%) (Table 1).

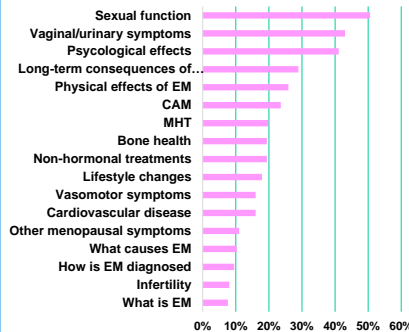
Table 1: Demographic characteristics of survey respondents

Characteristic	n (%)
Education (n=263)	
Year 12 or less	76(29)
Associate/Undergraduate diploma	78(30)
Post graduate diploma/Bachelor	78(30)
MSc/PhD	31(11)
Cause of EM (n=262)	
Cancer treatment	68(26)
Bilateral oophorectomy	80(31)
Autoimmune/Genetic/Metabolic/	37(14)
Others	
Unknown	77(29)
Time since diagnosis of EM (n=263)	
Less than 5 years ago	57(22)
5 or more years ago	206(78)
Location of residence (n=261)	
Metropolitan	145(55)
Regional	74(28)
Rural/Remote	42(16)

Results

Figure 1. Aspects of EM that women find difficult to talk to health professionals

Result expressed as proportion of women selecting this option



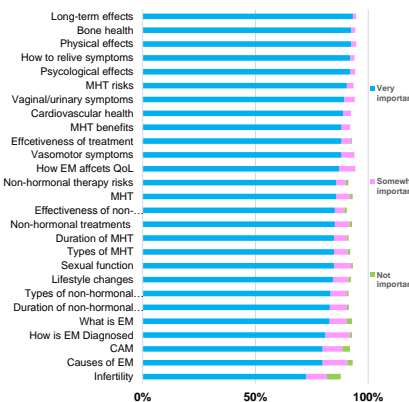
Note: CAM, Complementary and alternative medicines; MHT, Menopausal hormone therapy

Women reported greatest difficulty communicating with health professionals about sexual function, vaginal and urinary symptoms and psychological effects

Table 2. Women's attitudes to an EM QPL

Question	Responses (n=263)	n (%)
How helpful would a QPL be for EM	Not at all / a little	26 (10)
	Somewhat	89 (34)
	Very	139 (53)
How likely would you use a QPL for EM	Not at all likely / unlikely	40 (15)
	Neutral	43 (16)
	Likely or very likely	171 (65)
QPL useful to include in an EM website	Yes	166 (63)
	No	69 (26)

Figure 2. Attitudes of women towards inclusion of information in a QPL



Note: CAM, Complementary and alternative medicines; MHT, Menopausal hormone therapy

Over 80% of women considered diagnosis, symptoms, physical/psychological effects, long term implications, hormonal/non-hormonal management and lifestyle changes very important/essential to include in a QPL.

Associations between age, location, education, time since EM diagnosis and likelihood of using a QPL

- Older age was associated with being less likely to use a QPL (OR, 0.96, 95% CI, 0.93-0.98, p=0.004).
- The odds of being likely to use a QPL is increased in undergraduate diploma/vocational qualifications compared to year 12 or under (OR, 2.07, 95% CI, 1.02-4.20, p=0.04).
- There were no significant association between likelihood to use QPL and location (metropolitan versus non-metropolitan) or time since EM diagnosis.

Conclusion

- Many women with EM have difficulty communicating with health professionals. A comprehensive QPL would facilitate information sharing regarding EM.

Limitations:

- Potential response bias in relation to age/self-reported diagnosis of EM.
- Most of the participants had post-school qualifications

Future directions

The findings of this study have informed development of a QPL for women with EM which is currently under focus group testing. This QPL is a part of a translational program to develop evidence-based online resources for EM aiming to improve health outcomes.

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Women's perceptions regarding early menopause eHealth resources to facilitate self-care

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Background

Consumer knowledge gaps regarding early menopause (EM) (menopause before 45 years) potentially contribute to delayed diagnosis, variation in management and poorer outcomes⁽¹⁾. With continuing increases in digital device ownership, women are seeking electronic resources to facilitate knowledge access and enhance self-health management⁽²⁾, yet current EM related eHealth resources are either lacking or are inadequate for women's needs. We aimed to explore women's needs and perspectives regarding early menopause (EM) eHealth resources.

Methods

Participants Women with self reported diagnosis of EM aged >20 years were invited to participate in an online or paper survey.

Tool Data collection included: demographics, medical history, current use of electronic resources to manage health/EM, support for an App, desired features of the ideal App and EM information topics.

Exclusion criteria were No EM diagnosis, non-Australian residence and no English literacy.

Data analysis included descriptive statistics and logistic regression.

Results

Table 1: Demographic characteristics of survey respondents

Characteristic	n (%)
Education (n=263)	≤ Year 12 76(29)
	Associate/Undergraduate diploma 78(30)
	Post graduate diploma/Bachelor 78(30)
	MSc/PhD 31(12)
Cause of EM (n=262)	Cancer treatment 68(26)
	Bilateral oophorectomy 80(31)
	Autoimmune/Genetic/Metabolic/Others 37(14)
	Unknown 77(29)
Time since diagnosis of EM (n=263)	Less than 5 years ago 57(22)
	5 or more years ago 206(78)
Location of residence (n=261)	Metropolitan 145(55)
	Regional 74(28)
	Rural/Remote 42(16)

Results

Table 2. Electronic devices to manage health/EM

Question	n (%)
Electronic devices have access to	Mobile phone 42 (16)
	iOS smartphone (iPhone) 139 (52.9)
	Android smartphone 87 (33.1)
	Laptop 182 (69.2)
	Tablet/iPad 173 (66)
	Desktop Computer 167 (63.5)
Electronic devices used to manage health in the past	Mobile phone 8 (3)
	iOS smartphone (iphone) 77 (29.3)
	Android smartphone 43 (16.3)
	Laptop 116 (44.1)
	Tablet/iPad 102 (39)
	Desktop Computer 117 (44.5)
Electronic resource likely to use to manage EM	Electronic wearable fitness device 35 (13.3)
	Website 154 (59)
Used app before:	Mobile app 101 (38)
	To manage an aspect of EM 6 (2.3)
	To manage general health 64 (24.3)
	To manage another health condition 38 (14.4)

- Future menopause App use was less likely with increasing age (OR, 0.96; CI, 0.93-0.99, p=0.008). There were no significant associations with residential location, education, time since diagnosis, or cause of EM.
- **Features considered very important/essential to include in an EM App were:** evidence-based information (81%), question prompt list (78%), opportunities to ask an expert (76%) and ability to record symptoms/ health measures (67%).

Conclusion

Most women with EM have access to multiple electronic devices and are supportive of a comprehensive co-designed EM eHealth website or App with multiple features.

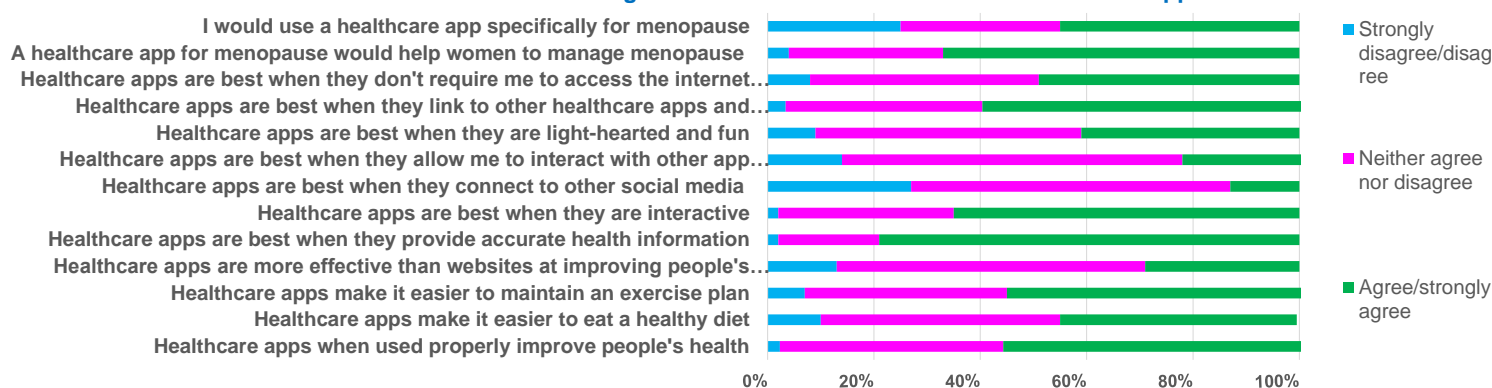
Limitations:

- Potential response bias in relation to age/self-reported EM diagnosis
- These findings may be less relevant to non- English speakers, women with lower literacy/ educational attainment and those without internet access.

Future directions

The results of this study will help development of high quality e-Health resources aiming to improve self-care and health outcomes. Broader engagement to address limitations, and we now aim to co-design resources, including user testing and evaluation.

Figure 1: Attitudes of women towards healthcare apps



References:

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Attitudes to and HRT prescribing practices

1. Are you in clinical practice currently? (select all that apply)

- ☐ I am not in clinical practice
 - ☐ Hospital based practice
 - ☐ Solo private/ general practice
 - ☐ Group (2 or more doctors) private/general practice
-

2. What is your age (years)?

[--Please Select--]

3. What is your gender?

- ☐ Male ☐ Female
-

4. How many years since you graduated from your medical degree?

5. What is your medical specialty?

- ☐ General practitioner
 - ☐ Endocrinologist
 - ☐ Obstetrician/Gynaecologist
 - ☐ Trainee/registrar- General practice
 - ☐ Trainee/registrar-Endocrinology
 - ☐ Trainee/registrar- Obstetrics/Gynaecology
 - ☐ If other, please specify
-

6. How many years have you been practising in this specialty?

7. What is the postcode of your main clinical practice (hospital or private practice office?)

8. Are you a member of a menopause society (select all that apply)?

- ☐ I am not a member of a menopause society
 - ☐ Australasian Menopause Society
 - ☐ North American Menopause Society
 - ☐ International Menopause Society
 - ☐ If other, please specify
-

9. I would assess my knowledge regarding particular aspects of menopause as:

	Menopause physiology	Hormone therapy	Non-hormonal therapy	Bone health	Cardiovascular disease	Metabolic syndrome
very knowledgeable and can teach others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
competently knowledgeable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knowledgeable but need to learn more	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Know nothing and need to learn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Know nothing and not my area of interest/practice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. To what extent do you agree with the following statement?

In general, HRT should be offered to menopausal women who have menopausal symptoms.

Strongly Agree Agree Neutral Disagree Strongly Disagree

☐ ☐ ☐ ☐ ☐

11. To what extent do you agree with the following statement?

In general, HRT should be offered to menopausal women who DO NOT have menopausal symptoms.

Strongly Agree Agree Neutral Disagree Strongly Disagree

☐ ☐ ☐ ☐ ☐

12. My preferred treatment for hot flushes is: (select one)

- ☐ HRT
 - ☐ Non-hormonal medication (eg venlafaxine, gabapentin)
 - ☐ Complementary and alternative therapy (eg herbal, acupuncture)
 - ☐ Compounded bio-identical hormone therapy
 - ☐ Lifestyle modification
 - ☐ If other, please specify
-

13. My preferred type of systemic (ie non-vaginal) HRT for women with premature menopause (menopause <40 years) without contraindications is: (select one)

- ☐ Combined oral contraceptive pill
 - ☐ Oral HRT
 - ☐ Transdermal patch or gel
 - ☐ Hormone Implant
 - ☐ Compounded bio-identical hormone therapy
 - ☐ I prefer not to use HRT.
 - ☐ If other, please specify
-
-

14. My preferred type of systemic (ie non-vaginal) HRT for women older than 50 years without contraindications is:
(select one)

- ☐ Oral
- ☐ Transdermal patch or gel
- ☐ Hormone Implant
- ☐ Compounded bio-identical hormone therapy
- ☐ I prefer not to use HRT.
- ☐ If other, please specify

15. I am personally using systemic HRT currently or my female partner is currently using systemic HRT. If yes , please specify which medication.

☐ Yes ☐ No

Additional Comments

16. The number of perimenopausal or postmenopausal women that I see as patients each week are:

[--Please Select--]

17. I would start systemic HRT (non-vaginal) for the following reasons: (select all that apply for each age range)

	If age < 40 years (premature menopause)	If age 40-49 years	If age 50-55 years	If age 56-60 years	If age >60 years
Relief of vasomotor symptoms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prevention of osteoporosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prevention of colon cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prevention or treatment of cognitive disorders	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Improve overall well-being	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Manage vaginal bleeding problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prevention of cardiovascular disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prevention of diabetes mellitus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reduced libido	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Atrophic vaginitis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anti-aging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dyspareunia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Incontinence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anxiety and/or depression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

18. How likely are you to prescribe systemic HRT to a menopausal women who has menopausal symptoms in the presence of the following conditions?

	Very likely	Likely	Neutral	Unlikely	Very unlikely
Personal history of breast cancer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Family history of breast cancer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Personal history of venous thrombosis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Family history of venous thrombosis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
History of cerebrovascular disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
History of ischaemic heart disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hyperlipidaemia	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hypertension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
History of uterine cancer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Diabetes mellitus	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Obesity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Patient has concern about breast cancer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

19. The preferred duration of systemic (non-vaginal) HRT for a WOMAN WITH PREMATURE MENOPAUSE is

- ☐ Total duration 1-5 years
☐ Total duration 6-10 years
☐ Total duration 11-15 years
☐ Until age 50-51 years
☐ Indefinite

20. The preferred duration of systemic (non-vaginal) COMBINED HRT (oestrogen +progesterone) for symptomatic women aged over 50 years is:

- ☐ Total duration 1-5 years
☐ Total duration 6-10 years
☐ Total duration 11-15 years
☐ Total duration >15 years
☐ Indefinite

21. The preferred duration of systemic (non-vaginal) OESTROGEN- ONLY HRT for symptomatic women without a uterus aged over 50 years is:

- ☐ Total duration 1-5 years
☐ Total duration 6-10 years
☐ Total duration 11-15 years
☐ Total duration >15 years
☐ Indefinite

22. To what extent do you agree with this statement?
I experience difficulty/ barriers to prescribing HRT.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

23. The difficulties/ barriers to prescribing HRT that I experience are: (select all that you consider relevant)

- ☐ I do not experience difficulties/ barriers to prescribing HRT
- ☐ I prefer not to prescribe HRT
- ☐ Time constraints when consulting to discuss HRT.
- ☐ Consumer concern regarding use of HRT and breast cancer.
- ☐ Consumer concerns regarding use of HRT and other (non breast cancer) potential risks.
- ☐ I do not consider the benefits of HRT outweigh the risks.
- ☐ Medicolegal consequences of prescribing HRT
- ☐ Difficulty explaining HRT risks and benefits to women
- ☐ Difficulty accessing HRT information for consumers.
- ☐ Lack of confidence in prescribing HRT
- ☐ Lack of suitable HRT products
- ☐ Consumer preferences for complementary/ alternative therapies
- ☐ If other, please specify

24. I find it easy to keep up with current HRT recommendations/ guidelines/evidence.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

25. My preferred method of obtaining up to date information about HRT is? (select one)

- ☐ Conference
- ☐ Specialist college website
- ☐ Menopause society website
- ☐ Medical magazine
- ☐ Journal article
- ☐ Pharmaceutical representative
- ☐ Webcast
- ☐ Email/ E news
- ☐ Government publication
- ☐ If other, please specify

26. Do you have any further comments regarding HRT?

Main Text

Title: Complementary medicine and alternative therapy use in women with early menopause

Short title: CAM use in early menopause

Word Count: Abstract – Main Text- 2295 (without tables and legend)

Table & Figure count: 4

Keywords

Complementary medicine, alternative therapy, early menopause, menopause

Abstract

Introduction: Complementary medicines and alternative therapy (CAM) use is common in menopausal women. However, CAM use by women with early menopause (EM), menopause before age 45, is unclear. This pilot study explored CAM use in women with EM compared to natural menopause.

Methods: Women aged >20 years were recruited from clinics and community. Self-reported menopausal status, symptoms (Greene Climacteric scale) and CAM use/perceptions were assessed via questionnaire. Data analysis included frequencies, T-test, Chi-square or Fisher exact tests and logistic regression analysis.

Results: EM women (n=27) were younger than natural peri/postmenopausal non-EM women (n=36); 34.6 ± 6.6 versus 53.5 ± 5.2 years ($p < 0.001$) and reported a cancer diagnosis (40% versus 8.8%; $p = 0.004$). CAM use differed between EM and non-EM groups. Meditation/mindfulness (52.2%) was the most common CAM used by EM women. Few (24%) EM women reported use of herbal CAM versus 51.6% non-EM women. Menopausal symptoms varied between groups; fewer women with EM reported “loss of interest in sex” (64% versus 91%; $p = 0.009$), or ‘sweating at night’ (70.5% versus 91.4%; $p = 0.045$). There was no significant association between CAM use and age/ menopausal symptoms. Most women (56.9%) agreed that “medical practitioners did not suggest CAM often enough”. Although, 51.6% of women disagreed that “CAMs do more harm than good”, 57.4% women were uncertain if CAM were “safer than prescribed medication”.

Discussion: CAM use and menopausal symptoms differ between EM and non-EM women. Consumer knowledge gaps exist regarding CAM use. This study highlights the need for increased CAM awareness and knowledge for both women and clinicians.

Introduction

Early menopause (EM) is menopause occurring before the age of 45, whereas the median age for natural menopause is 51 years ¹. Menopause is characterized by loss of ovarian function with resultant oestrogen deficiency accompanied by vasomotor symptoms (VMS), psychological symptoms, vaginal dryness and sleep disorders. About 40% of women seek medical advice for these symptoms².

Menopausal Hormone therapy (MHT) is regarded as the most effective treatment for menopausal symptoms ². However, there has been a significant decrease in the use of MHT since the Women's Health Initiative study was published in 2002, due to concerns regarding increased risk of breast cancer and cardiovascular disease (CVD) ³. Women seeking alternative treatment for their menopausal symptoms has led to a significant rise in women using Complementary and Alternative medicines (CAM)⁴. CAM use has been rising gradually all over the world, not only for menopausal symptoms but also for other health reasons.

CAM is defined as biologically based (botanicals, vitamins, minerals, fatty acids, compounded bio-identical hormone therapies, probiotics, whole diets and functional foods) mind-body, energy, manipulative and body-based therapies ⁵. Although CAM use has been investigated previously in older post-menopausal Australian women ⁶⁻⁹, there is limited data regarding CAM use in women with EM ^{5, 9}. A systematic review of worldwide prevalence of CAM use in menopausal women reported an average 12 month prevalence of CAM use of 47.7% ⁹. The aim of our pilot study is to explore CAM use in women with EM compared to natural menopause.

Methods

This was an observational, cross-sectional, questionnaire-based study involving women with a self-reported previous diagnosis of EM or natural age menopause. Participants aged 20 years or over, were recruited throughout Australia across a range of medical (Monash Health clinics, gynaecologist private practice) and community settings (Jean Hailes Foundation for Women and Monash University websites). The questionnaire was available in both paper and electronic form. Completion of the questionnaire was accepted as implied consent.

Questions were devised or adapted from previous studies of women with premature menopause^{10, 11} or CAM use^{6, 12, 13}. Data collection included self-reported menopausal status¹⁴, medical history including history of cancer, medications, CAMs, validated Greene Climacteric Scale (GCS)^{15, 16} to assess menopausal symptoms and perceptions regarding CAMs. CAM use was divided into body therapies, herbal therapies, vitamins and minerals and indication of use. The validated Greene Climacteric Scale (GCS)^{16, 17} was used to assess menopausal symptom experience. The GCS is a 21-item scale which asks, “The extent to which you are bothered at the moment” with answer options ranging from “not at all” to “extremely” (scored 0-3). Questionnaire was pilot tested in clinic with 10 patients to assess reliability. Exclusion criteria were women unable to read English or provide consent. This research was approved by the Monash Health Human Research Ethics Committee (project 07062A). Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0. Categorical data are presented as count and proportions, with groups compared using Chi-square tests or Fisher exact tests. Continuous data are presented as mean \pm standard deviation and groups compared using an independent t-test. A logistic regression model was used to measure the

association of independent variables such as age, education and menopause symptoms with CAM use. A P-value <0.05 was considered statistically significant.

Results

Participant characteristics

Of 78 women recruited, 63 were included in the final analysis. Incomplete responses to various components of the questionnaire including unknown status of menopause were reasons for exclusion. EM diagnosis was reported by 27 women and 36 were natural age peri/post menopause (classified “non-EM”). Demographic and medical history characteristics are shown in Table 1. Women with EM were significantly younger (34.6 ± 6.6 years) than non-EM women (53.5 ± 5.2 years; $p < 0.001$). Most women (>70%) had completed higher education (Diploma/ University degree) with no difference between groups. Significantly fewer women in the EM group (50.0%) were parous compared to the non-EM group (75.0%; $p = 0.042$). More women with EM reported a cancer diagnosis (40.0%) compared to the non-EM group (8.8%; $p = 0.004$). More than 90% of women in both groups were non-smokers. MHT/ oral contraceptive pill (OCP) use was significantly higher in women with EM (74.1% versus 31.4%; $p = 0.001$).

Menopausal Symptoms

Menopausal symptoms assessed by the GCS were commonly reported by women in both groups (Table 2). Symptoms most commonly reported by women with EM were “feeling tired” (85.2%), “muscle and joint aches and pains” (77.8%), “difficulty sleeping” (77.8%), “irritability” (73.1%) and VMS (70.4%). More women in the EM group reported “crying spells” (59.3% versus 29.4%; $p = 0.019$). However, fewer women with EM reported “Loss of interest in most things” (66.7% versus 91.4%; $p = 0.014$), “loss of

interest in sex” (64.0% versus 91.4%; $p=0.009$) and ‘sweating at night’ (70.5 versus 91.4%; $p=0.045$) compared to non-EM women.

Complementary medicine use

Mind and Body therapies

CAM use was divided into body therapies, herbal therapies, vitamins and minerals.

The proportion of women with EM using mind and body therapies varied from 0% (reflexology or paced respiration) to 52.2% (mindfulness/meditation) (Table 1A).

Relaxation and mindfulness/meditation, were the commonest mind-body therapy currently used in both groups (Table 3A). Previously used therapies that were most commonly reported by EM women were yoga, naturopathy and chiropractor. None of the women in the EM group described currently using homeopathy, aromatherapy, shiatsu or cognitive behaviour therapy, although these therapies had been previously used by women with EM.

The proportion of non-EM women reporting use of mind body therapies varied from 17.2% (paced respiration) to 62.5% (yoga). More women in the non-EM group reported previously using acupuncture compared with women with EM ($p=0.02$). Although no women with EM reported use of paced respiration and reflexology, 17.2% and 23.3% non-EM women reported current and previous use respectively.

Herbal and botanical therapies

Less than 25% of women with EM reported current or previous use of herbal/botanical therapies (Table 3B). Turmeric and soy products were most commonly used in both groups. Evening primrose oil (24.0%) and chasteberry (17.4%) were the commonest herbal/botanical therapies reported as previously used by women with EM. Fewer EM women previously used black cohosh compared to non-EM women ($p=0.001$).

The proportion of non-EM women reporting use of herbal/botanical therapies varied from 3.4% (dong quai) to 51.6% (black cohosh and evening primrose oil).

Vitamins and Minerals

Vitamin D was the most common vitamin/mineral supplement with 88% of women with EM and 65.6% of women with non-EM reporting use (Table 3C). Current use of calcium and multivitamin was reported by 50.0% and 30.4% of women with EM and 31.3% and 37.9% of non-EM women. More non-EM women (34.3%) reported previous use of glucosamine than EM women 9.5%; $p=0.038$) but current use was similar.

Association between CAM use and menopausal symptoms

There was no significant association between any CAM use and age, education or menopausal symptoms (data not shown).

Perceptions regarding CAM

Women's perceptions regarding CAM use and prescription medicines are shown in Figure 1. Most women perceived that "medical practitioners did not suggest CAM often enough" and "put too much trust in prescription medication". Although, 51.6% of women disagreed that "CAMs do more harm than good", 57.4% women were uncertain if CAM were "safer than prescribed medication".

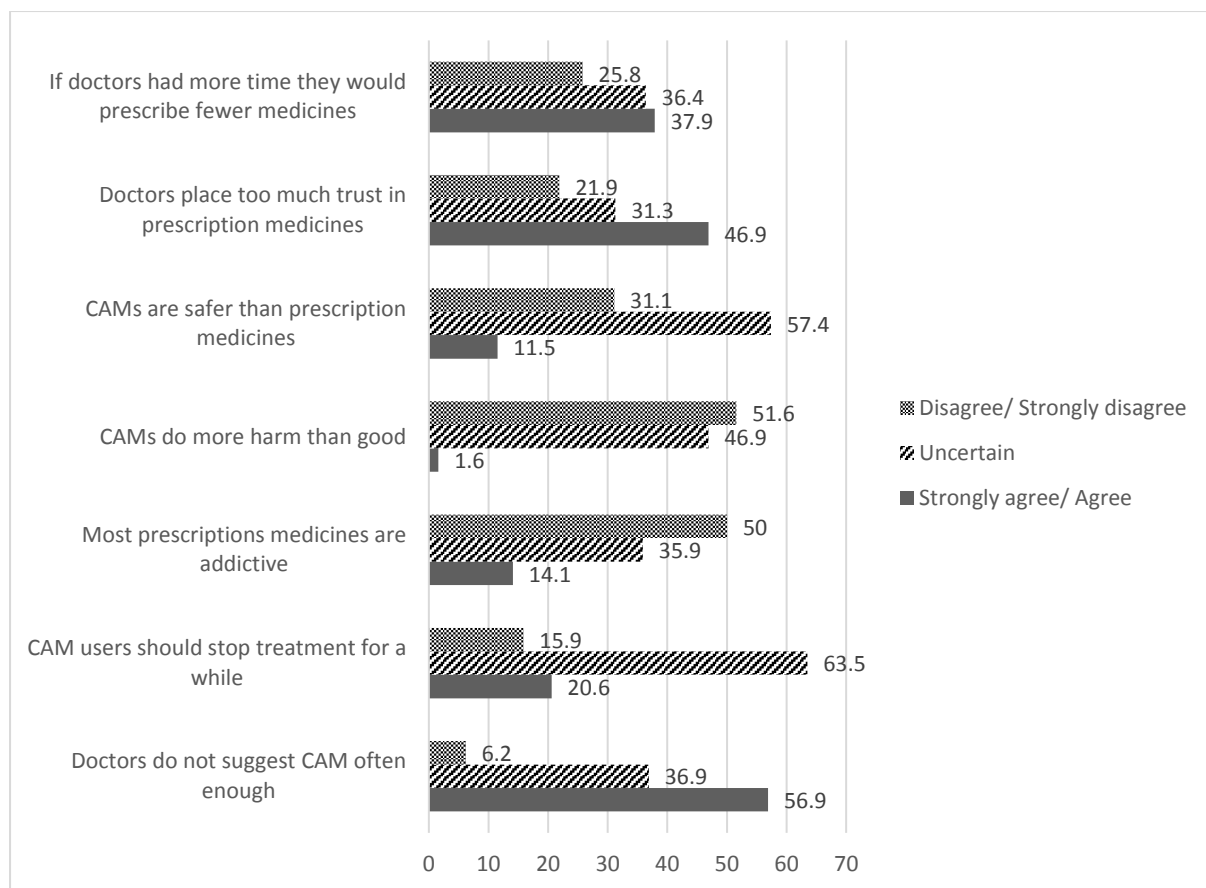


Figure 1: Women's perceptions regarding complementary medicines.
Results expressed as percentage of all women selecting option using a Likert scale.

Discussion:

There has been an increase in CAM use across all ages over the past decades ^{17, 18}.

The prevalence of self-reported CAM use by Australian mid-life women reported in previous studies ranges from 62.5% to 82% of 886 women aged 48-67 years ^{6, 19}.

The Australian Longitudinal Study on Women's Health (ALWHS) indicated that 75% of women aged 59-64 years (n= 10011) reported CAM⁷ use compared to 12% of women using MHT. Furthermore, 39% of menopausal women had consulted a CAM practitioner^{4, 7}. CAM use was reported by 55-72% of women with premature menopause or premenopausal controls ⁵. The reported prevalence of CAM use for menopausal symptoms by Australian women with breast cancer was 6.4%

(n=1588)¹². Our study is consistent with these findings where up to 52% of EM women and 65% of non-EM women were currently using or had tried a CAM. The spectrum of menopausal symptoms differed between the two groups with fewer EM women reporting VMS or “loss of interest in sex”. Our findings are similar to a community study of Australian women¹⁶ which reported more VMS in the perimenopausal group and lower libido in women aged 50-69 years using the GCS. The differences in menopausal symptoms reported by women with EM versus non-EM group may also reflect that more women in EM group reported use of MHT/OCP where oestrogen use has been shown to improve menopausal symptoms^{20, 21}. The lack of association between menopausal symptoms and CAM use may reflect the small sample size of this study and indicates the need for further research.

Mindfulness/meditation was the most commonly practiced mind/body therapy amongst both groups reported by >50% of women. This may relate to the ability to be self-prescribed, low cost and relatively easy to practice. The Australian Longitudinal Women’s Health Study observed significant associations between CAM and menopausal status; yoga/meditation was more commonly used by women with natural versus surgical menopause ($p<0.001$)⁷. In our study we grouped mindfulness/meditation together and yoga as separate therapy. Although mindfulness/meditation was the most common therapy used by both groups, only 35% women in EM group reported current/previous yoga practice.

Phytoestrogens and primrose oil were the most frequent herbal CAM used by both groups. This is consistent with a previous study⁹ of 2020 Australian women aged 40-65 years, which reported that phytoestrogens were most commonly used for VMS (6.29%) followed by evening primrose oil (3.91%). A higher prevalence of herbal therapies use (38-52%) was reported in a previous study of 54 women with

premature menopause, which may relate to a lower prevalence of cancer diagnosis (13/54 women)⁵, where the safety of herbal therapies in the setting of cancer is uncertain. There is mixed evidence regarding the efficacy of phytoestrogens, for VMS^{22 23}.

Calcium, vitamin D and multivitamin use was common in both groups. This is likely due to awareness regarding osteoporosis prevention for post-menopausal women²⁴. Fish oil supplements were more commonly used in the non-EM group which may reflect perceived benefits regarding CVD. However, a recent meta-analysis of 10 trials involving 77,917 individuals showed no benefit of omega-3 fatty acid supplement use with CVD risk²⁵. This highlights the need for further research to clarify the evidence for CAM therapies for health benefits.

Our study highlights that although women may use CAMs, they are uncertain regarding their safety. A study by Gibson-Helm et al of women with premature menopause reported differences in understanding of various menopausal therapies amongst women with differing aetiologies for premature menopause. Although 38-53% of women with premature menopause reported herbal CAM use, >60% of women reported a lack of knowledge regarding herbal therapies⁵. As with our study, the authors observed that women used a combination of CAM and prescription medication which may lead to potential interactions. This highlights the knowledge gaps that exist regarding CAM safety and efficacy and indicates the need for increased consumer awareness and education.

The finding that >50% of women perceived that “doctors do not suggest CAM enough” is interesting. Gollschewski et al found similar results where women reported negative experience with doctors in regards to CAM or doctors are ‘only interested in hormone therapy’²⁶. A study by Yeganeh et al investigated Australian

health practitioners (HP) knowledge and attitudes regarding MHT ²⁷. They found that although majority of HP's would consider prescribing MHT for symptomatic relief, younger and newer graduates reported more knowledge regarding non-hormonal therapies. This highlights HP's knowledge gaps regarding non-hormonal therapies and barriers to prescribing MHT including both clinician and consumer factors. This may contribute to increasing use of self-prescribed CAM. There is also a lack of communication regarding CAM use between women and their HP's ⁴ where HP's do not enquire about CAM use and women do not volunteer this information. This indicates a need for increased awareness/ knowledge for clinicians regarding CAM with the potential to incorporate evidence-based use of CAM. Quality research in this area is needed to support this evidence base.

Limitations & Strengths

The strengths of this study are: (i) study design comparing women with EM versus older women; (ii) extensive list of CAMs investigated and (iii) use of validated scales. We acknowledge that the limitations of this study including small sample size, due to difficulties with recruitment, and self-reported menopausal status.

Conclusions:

This pilot study investigating CAM use in Australian women with EM indicates a variable use. The pattern of CAM use and menopausal symptoms differed from women without EM. This study also highlights the need for increased awareness of CAM therapies amongst both women and clinicians.

Table 1: Demographics and medical history characteristics of women in early and non-early menopause groups.

Characteristic	EM N (%) or mean \pmSD	Non-EM N (%) or mean \pmSD	P Value*
Age	34.6 \pm 6.6	53.5 \pm 5.2	<0.001
Children Yes	13/26 (50.0)	27/36 (75.0)	0.040
Education			
• Primary/High School/Secondary	3/26 (11.5)	10/36 (27.8)	0.280
• Diploma/Tafe	12/26 (46.2)	12/36 (33.3)	
• University	11/26 (42.3)	14/36 (38.9)	
Smoking Yes	2/26 (7.7)	1/35 (2.9)	0.570
History of Depression	10/25 (40.0)	15/34 (44.1)	0.750
History of Osteoporosis	5/25 (20.0)	2/34 (5.9)	0.120
History of Cancer	10/25 (40.0)	3/34 (8.8)	0.004
MHT/OCP use	20/27 (74.1)	11/35 (31.4)	0.001

*T test, Chi-square test or Fisher's exact test. Data is presented as frequencies (N) and percentages (%).

Table 2: Proportion of women reporting menopause symptom bother from ‘not at all’ to ‘extremely’ (using the Greene Climacteric scale).

	EM N (%)	Non-EM N (%)	P Value*
Heart beating quickly or strongly	13/27 (48.1)	15/ 34 (44.1)	0.750
Feeling tense or nervous	18/27 (66.7)	28/34 (82.4)	0.160
Difficulty sleeping	21/27 (77.8)	32/36 (88.9)	0.300
Excitable	12/25 (48.0)	12/33 (36.4)	0.370
Attacks of panic	12/27 (44.4)	11/ 34 (32.4)	0.330
Difficulty concentrating	18/27 (66.7)	28/35 (80.0)	0.230
Feeling tired or lacking in energy	23/27 (85.2)	29/35 (82.9)	1.000
Loss of interest in most things	18/27 (66.7)	32/35 (91.4)	0.010
Feeling unhappy or depressed	16/27 (59.3)	26/35 (74.3)	0.210
Crying spells	16/27 (59.3)	10/34 (29.4)	0.020
Irritability	19/26 (73.1)	27/34 (79.4)	0.570
Feeling dizzy or faint	15/26 (57.7)	11/ 34 (32.4)	0.050
Pressure or tightness in head or body	14/27 (51.9)	15/34 (44.1)	0.550
Parts of body numb or tingling	15/27 (55.6)	20/36 (55.6)	1.000
Headaches	17/27 (63.0)	19/33 (57.6)	0.670
Muscle and joint pains	21/27 (77.8)	26/35 (74.3)	0.750
Loss of feeling in hands or feet	10/27 (37.0)	15/34 (44.1)	0.580
Breathing difficulties	8/27 (29.6)	10/34 (29.4)	0.990
Hot flushes	19/27 (70.4)	31/36 (86.1)	0.130
Sweating at night	19/27 (70.4)	32/35 (91.4)	0.040
Loss of interest in sex	16/25 (64.0)	32/35 (91.4)	0.009

*Statistical analysis used Chi-square or Fisher’s exact test. Data is presented as frequencies (N) and percentages (%).

Table 3: Current and previous use of different types of CAM by women with early (EM) and non-early menopause (Non-EM) groups. CAM are grouped as Mind and Body therapies (Table 3A), Herbal/Botanical therapies (Table 3B) and Vitamins and Minerals (Table 3C).

Table 3A: Mind Body Therapies			
Therapy	EM N (%)	Non-EM N (%)	P value*
Acupuncture			
Current	2/22 (9.1)	2/33 (6.1)	1.000
Previous	2/22 (9.1)	12/33 (36.3)	0.020
Chiropractor			
Current	1/20 (5.0)	4/31 (12.9)	0.640
Previous	4/20 (20.0)	6/31 (19.4)	0.950
Homeopathy			
Current	0/19 (0)	2/31 (6.5)	0.520
Previous	2/19 (10.5)	5/31 (16.1)	0.700
Osteopathy			
Current	1/20 (5.0)	1/31 (3.2)	1.000
Previous	2/20 (10.0)	9/31 (29.0)	0.100
Reflexology			
Current	0/18 (0)	2/30 (6.7)	0.520
Previous	0/18 (0)	5/30 (16.7)	0.140
Aromatherapy			
Current	0/19 (0)	3/27 (11.1)	0.260
Previous	3/19 (15.8)	3/27 (11.1)	0.680
Naturopathy			
Current	1/19 (5.3)	3/32 (9.4)	1.000
Previous	4/19 (21.1)	8/32 (25.0)	0.750
Shiatsu			
Current	0/20 (0)	2/30 (6.7)	0.510
Previous	1/20 (5.0)	4/30 (13.3)	0.640
Reiki			
Current	1/19 (5.3)	3/31 (9.7)	1.000
Previous	0/19 (0)	5/31 (16.1)	0.140
Yoga			
Current	2/20 (10.0)	8/32 (25)	0.180
Previous	5/20 (25.0)	12/32 (37.5)	0.350
Mindfulness/ Meditation			
Current	8/23 (34.8)	14/33 (42.4)	0.570
Previous	4/23 (17.4)	6/33 (18.2)	0.940
Paced respiration			
Current	0/20 (0)	3/29 (10.3)	0.260
Previous	0/20 (0)	2/29 (6.9)	0.510
Relaxation			
Current	8/22 (36.4)	12/29 (41.4)	0.720
Previous	1/22 (4.5)	5/29 (17.2)	0.220
Cognitive Behaviour Therapy			
Current	0/21 (0)	3/31 (9.7)	0.260
Previous	2/21 (9.5)	5/31 (16.1)	0.690

Statistical analysis used Chi-square or Fisher's exact test. Data is presented as frequencies and percentages (%)

Table 3B: Herbal/ Botanical Therapies			
Therapy	EM N (%)	Non-EM N (%)	P Value*
Black Cohosh			
Current	0/24(0)	1/31(3.2)	1.000
Previous	2/24(8.3)	15/31(48.4)	0.001
Primrose Oil			
Current	1/25(4.0)	2/31(6.5)	1.000
Previous	6/25(24.0)	14/31(45.2)	0.100
Soy Products			
Current	3/23(13.0)	5/29(17.2)	1.000
Previous	2/23(8.7)	6/29(20.7)	0.280
Red Clover			
Current	1/23(4.3)	3/32(9.4)	0.630
Previous	2/23(8.7)	10/32(31.3)	0.040
St. John's wart			
Current	0/24(0)	3/30(10.0)	0.250
Previous	3/24(12.5)	3/30(10.0)	1.000
Ginseng			
Current	0/21(0)	0/31(0)	-
Previous	0/21(0)	3/31(12.9)	0.140
Dong Quai			
Current	1/22(4.5)	0/29(0)	0.430
Previous	2/21(9.5)	1/29(3.4)	0.570
Chasteberry			
Current	1/23(4.3)	1/30(3.3)	1.000
Previous	4/23(17.4)	2/30(6.7)	0.220
Licorice			
Current	0/21(0)	1/32(3.1)	1.000
Previous	1/21(4.8)	6/32(18.8)	0.220
Turmeric			
Current	4/23(17.4)	7/29(24.1)	0.550
Previous	0/23(0)	5/29(17.2)	0.060
Sage			
Current	0/21(0)	0/29(0)	-
Previous	2/21(9.5)	6/29(20.7)	0.440
Valerian			
Current	0/22(0)	0/30(0)	-
Previous	1/22(4.5)	6/30(20.0)	0.220

Statistical analysis used Chi-square or Fisher's exact test. Data is presented as frequencies and percentages (%).

Table 3C: Vitamins and Minerals			
Therapy	EM N (%)	Non-EM N (%)	P value*
Fish Oil			
Current	5/23 (21.7)	12/33 (36.4)	0.240
Previous	5/23(21.7)	8/33(24.2)	0.830
Glucosamine			
Current	3/21 (14.3)	5/35 (14.3)	1.000
Previous	2/21(9.5)	12/35 (34.3)	0.040
Calcium			
Current	11/22 (50.0)	10/32 (31.3)	0.170
Previous	6/22 (27.3)	8/32 (25.0)	0.850
Vitamin D			
Current	16/25 (64.0)	14/32 (43.8)	0.130
Previous	6/25 (24.0)	7/32 (21.9)	0.850
Multivitamin			
Current	7/23 (30.4)	11/29 (37.9)	0.570
Previous	7/23 (30.4)	5/29 (17.2)	0.260
Coenzyme Q10			
Current	0/19 (0)	2/29 (6.9)	0.510
Previous	2/19 (10.5)	9/29 (31.0)	0.090

Statistical analysis used Chi-square or Fisher's exact test. Data is presented as frequencies and percentages (%).

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Management of bone health in women with premature ovarian insufficiency: Systematic appraisal of clinical practice guidelines and algorithm development

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ABSTRACT

Background: Osteoporosis is a key concern of women with premature ovarian insufficiency (POI) but there are gaps in clinicians' knowledge of bone health.

Objectives: 1) To systematically evaluate the quality of clinical practice guidelines (CPGs) related to POI and bone health; 2) to formulate a management algorithm.

Methods: Systematic search for English-language clinical practice guidelines (CPGs) from August 2012 to August 2017 (PROSPERO registration number CRD42017075143). Four reviewers independently evaluated the methodological quality of included CPGs using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (comprising 23 items across 6 domains) using the My AGREE PLUS platform. Inter-rater reliability was assessed using the intraclass correlation coefficient (ICC). Individual domain and total percentage scores were calculated for each CPG. Data from high-scoring CPGs were extracted and summarised to develop the algorithm, with subsequent refinement via expert and end-user clinician feedback.

Results: The systematic search yielded 16 CPGs for appraisal. ICC values were 0.71 (good) to 0.95 (very good). The quality of the CPGs was appraised as "high" in 4 cases, "average" in 8 and "low" in 4. High-quality CPGs had mean total scores of 82–96%. Recommendations from high-quality CPGs were summarised into 6 categories: screening; risk factors; initial assessment; diagnosis; subsequent assessment; and management. Only "management" had recommendations (moderate-quality to low-quality evidence) from all four high-quality CPGs. Limitations are reflected in the algorithm.

Conclusions: Most CPGs regarding bone health and POI are of average to poor quality. High-quality CPGs have evidence limitations and recommendation gaps indicating the need for further research.

1. Introduction

Premature Ovarian Insufficiency (POI) can be spontaneous or iatrogenic and is defined as loss of ovarian function with development of hypergonadotropic hypogonadism in women under the age of 40 years [1]. Spontaneous POI affects approximately 1% of women and is associated with genetic defects, autoimmune disorders, environmental factors and infections, but is most commonly idiopathic [2,3].

Iatrogenic POI can occur secondary to surgical intervention (E.g. bilateral oophorectomy), chemotherapy and/or radiotherapy [2,4].

The effects of oestrogen deficiency include menopausal symptoms such as: vasomotor symptoms, insomnia, mood lability, and vulvo-vaginal atrophy. Longer-term consequences of POI include an increased risk of cardiovascular disease and mortality, accelerated cognitive impairment, infertility and osteoporosis [2,4–6]. Women with POI have a significantly lower bone mineral density (BMD) [2,4,7–13] and a 1.5–

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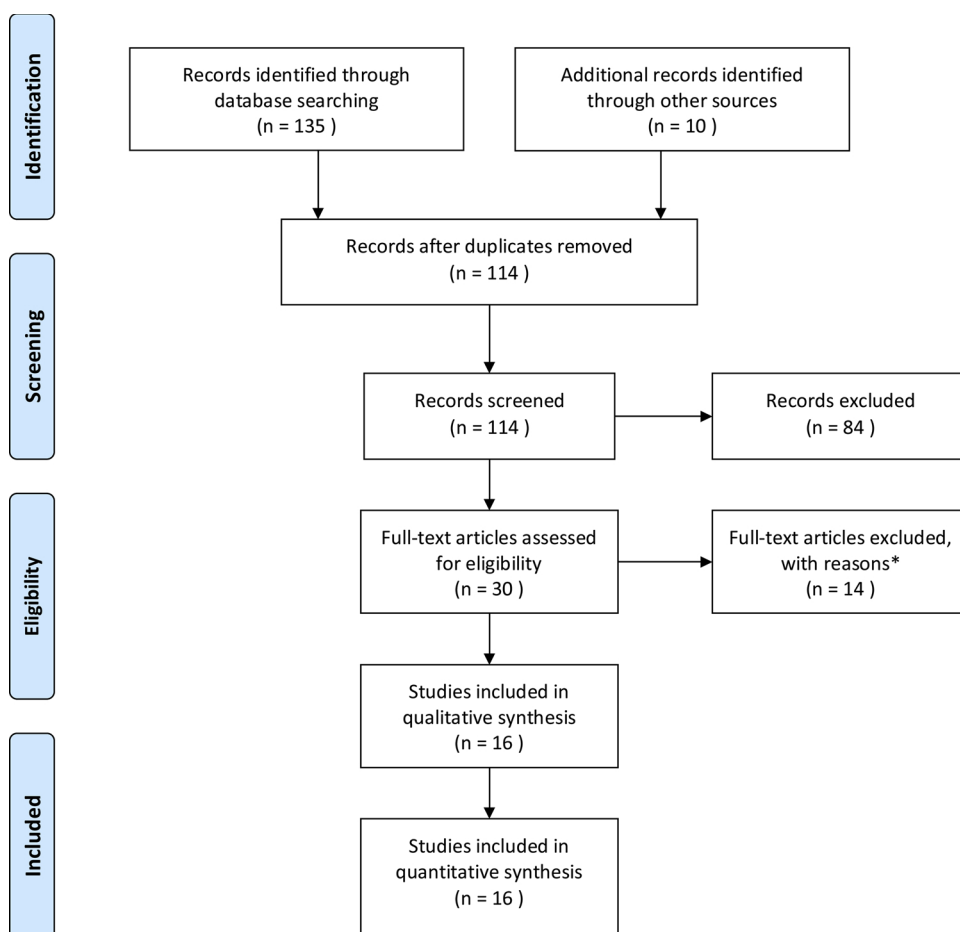


Fig. 1. PRISMA flow diagram of included studies.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:<https://doi.org/10.1371/journal.pmed1000097>.

*Reasons for exclusion: wrong patient population (n = 6), not a CPG (n = 5), superseded by updated guidelines (n = 2), summary of full CPG (n = 1).

fold greater risk of fracture compared to women who experience menopause at the typical age [14–16].

The estimated prevalence of osteoporosis in women with POI is approximately 8–14% [2,13]. Sex-steroids contribute to skeletal homeostasis during growth and adulthood. Bone loss starts after achieving peak bone mass regardless of changes in sex steroid concentrations but the sharp decline of oestrogen levels at menopause accelerates bone loss and leads to deterioration in bone micro-architecture [7,8].

Clinical practice guidelines (CPGs) are being increasingly used by clinicians to assist patient management [17–20]. They encompass statements to aid clinicians' decisions regarding appropriate care for specific clinical circumstances [17,18]. The benefits of using CPGs can include improved consistency of care and quality of clinical decisions by offering recommendations for clinicians who are uncertain how to proceed, updating outdated practices and providing reassurance about appropriateness of treatment based on authoritative recommendations [19]. Adherence to CPGs has been shown to improve the process of care as well as patient outcomes [20]. However, implementation of poor-quality guidelines may be detrimental to the patient and the health care system [17,18]. Many existing CPGs lack high-quality evidence and rigorous methodology, compromising their integrity [17,18,21].

Women with POI are cared for by a variety of clinicians whom are not necessarily specialists in bone health including primary care providers, gynecologists and endocrinologists. High-quality CPGs could be useful to simplify decision-making and provide more consistent care for these women. To date, there are numerous publications related to managing bone health in women with POI derived from varying sources, which are of unknown quality [1,2,21–36]. This may contribute to the observed variations in clinical practice and clinician

knowledge gaps regarding management of POI, including bone health [37].

The aim of this study was to review the methodological quality of contemporary CPGs regarding bone health in women with POI and, using these findings, formulate a management algorithm to guide treating clinicians.

2. Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered with The International Prospective Register Of Systematic Reviews (PROSPERO) (Registration number CRD42017075143). A systematic review was conducted of contemporary CPGs in which management of bone health in POI was addressed.

2.1. Search methods for identification of guidelines

A comprehensive search of electronic databases, guideline repositories, the websites of relevant professional societies and the grey literature was conducted (Supplement 1). The bibliographies of retrieved guidelines were manually reviewed for identification of additional potentially relevant guidelines.

The search was conducted in August and September 2017. A sensitive search strategy was used, combining relevant subject indexing and free text terms for “guideline”, “premature ovarian insufficiency” and “bone”. The search was limited to English language, human subjects and publication date of August 2012 to August 2017. The detailed search strategy is provided in Supplement 2.

MANAGEMENT ALGORITHM FOR BONE HEALTH IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY (POI)

Women with Premature Ovarian Insufficiency

Initial Bone Health Evaluations		
Potential risk factors for low BMD[‡] with POI <ul style="list-style-type: none"> • Primary amenorrhoea. • Longer duration of POI • >1yr delay in diagnosis. • Age <20 years at onset of irregular menses • Childhood cancer survivors with hypogonadism and: <ul style="list-style-type: none"> - Hypothyroidism AND growth hormone deficiency. - Previous treatment with: chemotherapy/ glucocorticoids (higher cumulative dose/ - Cranial irradiation. - Caucasian ethnicity. 	General risk factors for low BMD[‡] <p>Non-modifiable</p> <ul style="list-style-type: none"> • Age. • Prior fragility fracture. • Family history of osteoporosis. • Parental history of fracture. <p>Modifiable and lifestyle</p> <ul style="list-style-type: none"> • Height loss > 3cm • Multiple falls. • Low physical activity or immobility. • Low body weight (body mass index <18 kg/m²) • Low muscle mass and strength. • Poor balance. • Vitamin D insufficiency. • Protein or calcium undernutrition. • Smoking. • Alcohol >2 standard drinks/day. 	Diseases associated with low BMD[‡] +/- POI <ul style="list-style-type: none"> • Rheumatoid arthritis. • Hyperthyroidism. • Hyperparathyroidism. • Chronic kidney disease. • Coeliac disease or malabsorption. • Diabetes mellitus. • Myeloma or MGUS.[#] • Bone marrow/ organ transplant. • HIV[#] infection. • Depression. <p>Medications associated with low BMD[‡]</p> <ul style="list-style-type: none"> • Glucocorticoids. • Excess thyroid hormone replacement. • Aromatase inhibitors.
Blood and urine tests <ul style="list-style-type: none"> • UEC, CMP, LFT, TSH, 25-hydroxy vitamin D[‡] • Bone turnover markers: not currently recommended for routine use. • If reduced bone mass is present, also consider the following: serum PTH[‡], coeliac serology, serum electrophoresis and 24-hour urine calcium excretion. 	Imaging <ul style="list-style-type: none"> • DXA: Indicated at initial diagnosis for all women with POI, especially if long duration of oestrogen deficiency or other risk factors for osteoporosis. Guidelines suggest the use of Z score <-2 to define low bone mass and T scores <-2.5 to define osteoporosis. 'Low bone mass' is the preferred term in this setting rather than osteopenia.^{1,2} • Plain imaging: Lateral radiographs of lumbar and thoracic spine or DXA-based Vertebral Fracture Assessment (VFA) should be considered on an individual basis particularly if concerns regarding height loss, back pain, chronic diseases associated with low BMD[‡] and current or past glucocorticoid use. 	

Management		
Maintain healthy lifestyle (Low-moderate quality evidence) <ul style="list-style-type: none"> • Weight-bearing exercise. • Avoidance of smoking. • Maintenance of normal body weight. • Balanced diet containing the recommended intake of calcium and vitamin D – dietary supplements may be required if inadequate intake. • Avoid excess alcohol. 	Hormone replacement therapy (Low-moderate quality evidence) <ul style="list-style-type: none"> • Offer oestrogen replacement therapy in all women diagnosed with POI unless contraindicated. • Both HRT[#] and OCP[#] are appropriate but OCP[#] has less favourable effects on bone protection. HRT containing 17β-oestradiol also known as Oestradiol (E2) is preferred for oestrogen replacement. • Give combined treatment with progesterone to women with intact uterus. • Consider patient preference for route and method of administration as well as contraceptive needs. • Continue hormone replacement until at least the time of anticipated natural menopause (approx. 50yo), then reassess. 	Anti-resorptive therapy (Low-moderate quality evidence) <ul style="list-style-type: none"> • Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist.

Further Assessment	
Subsequent assessment of bone health <ul style="list-style-type: none"> • If BMD[‡] is normal and adequate systemic oestrogen replacement is commenced, the value of repeated DXA[‡] scan is low. • If a diagnosis of low bone mass is made and oestrogen replacement or other therapy initiated, repeat DXA[‡] in 2-5 years. 	Specialist referral <ul style="list-style-type: none"> • A decrease in BMD[‡] on subsequent scans (bone loss >5% and/or >0.05g/cm²) should prompt review of oestrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate. • Development of a fragility fracture should prompt referral to an osteoporosis specialist.

[‡] FRAX risk calculator is not validated for use in women < 40 years

[#] BMD – Bone mineral density, MGUS – Monoclonal gammopathy of undetermined significance, HIV – Human immunodeficiency virus, CMP – Calcium, magnesium, phosphate, UEC – Urea, electrolytes, creatinine, LFT – Liver Function tests, TSH – Thyroid stimulating hormone, PTH – Parathyroid hormone, HRT – Hormone replacement therapy, OCP – oral contraceptive pill, FRAX – Fracture risk assessment tool

1. ESHRE Guideline Group on POI, et al. "ESHRE Guideline: management of women with premature ovarian insufficiency." *Human Reproduction* 31.5 (2016): 926-937.

2. Ferrari, S., et al. "Osteoporosis in young adults: pathophysiology, diagnosis, and management." *Osteoporosis International* 23.12 (2012): 2735-2748

(caption on next page)

Fig. 2. Management algorithm.

† FRAX risk calculator is not validated for use in women < 40 years.

BMD – Bone mineral density, MGUS – Monoclonal gammopathy of undetermined significance, HIV – Human immunodeficiency virus, CMP – Calcium, magnesium, phosphate, UEC – Urea, electrolytes, creatinine, LFT – Liver Function tests, TSH – Thyroid stimulating hormone, PTH – Parathyroid hormone, HRT – Hormone replacement therapy, OCP – oral contraceptive pill, FRAX – Fracture risk assessment tool.

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2.2. Eligibility criteria and selection process

Two independent reviewers (SDC and AV) screened the titles and abstracts of the retrieved records to identify their eligibility for inclusion. The latest version of national and international CPGs, recommendations, position statements, consensus statements and development conferences, which provided guidance on osteoporosis prevention and management in women with POI or early menopause were included. We excluded systematic reviews, randomised controlled trials (RCTs), controlled (non-randomised) clinical trials, case-control, prospective and retrospective cohort and cross-sectional studies, case reports, pilot and feasibility studies, narrative reviews, scientific reports, commentaries, conference abstracts and posters. Selected guidelines were reviewed to verify eligibility (Fig. 1). Guidelines were excluded if they included women with menopause diagnosed after age 45 years. Any disagreement was resolved by discussion to reach consensus.

2.3. Quality assessment

The quality of the guidelines was evaluated using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument [38]. This instrument is designed to appraise the quality of health-related CPGs by evaluating the methodological quality. It consists of 23 items organized in six domains: 1) Scope and Purpose (items 1–3), 2) Stakeholder Involvement (items 4–6), 3) Rigor of Development (items 7–14), 4) Clarity of Presentation (items 15–17), 5) Applicability (items 18–21) and 6) Editorial Independence (items 22–23), with each item rated on a seven-point Likert scale [38]. A score of 1 was given for strongly disagree, 2–6 indicating the full criteria has not been met and 7 meant strongly agree indicating that the quality of reporting is exceptional, and all criteria and consideration articulated in the user's manual were met. These six domains are followed by two additional items forming an Overall Assessment, which includes “the rating of the overall quality of the guidelines and whether the guidelines would be recommended for use in practice” [38].

Four independent reviewers (SDC, AV, GS and FM) scored each of the CPGs according to the AGREE II instrument via the My Agree Plus online platform, which they had been trained to use through the user manual [38]. Total scores for each domain were calculated by summing up the scores of the individual items within the domain and scaling them as a percentage of the maximum possible score for that domain, expressed as mean \pm Standard Deviation (SD) [38]. Similar to previous studies, the quality of CPGs was defined as follows: high-quality when 5 or more domains scored > 60%, average-quality when 3 or 4 domains scored > 60%, low-quality when ≤ 2 domains scores > 60% [30,39].

2.4. Data analysis

Descriptive statistics was performed using Microsoft Excel 2013 (Redmond, Washington, USA). The inter-rater reliability analysis was performed to assess the degree of agreement between reviewers using the intraclass correlation coefficient (ICC) with a 95% confidence interval (CI). The scores were defined as: poor 0.0–0.2, fair 0.21–0.4, moderate 0.41–0.6, good 0.61–0.8 and very good 0.81–1.00. Where the ICC < 0.70, domain scores were discussed by the reviewers and a

consensus made. The reliability analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0.

2.5. Development of the algorithm

Recommendations specifically related to women with POI from the highest scoring CPGs were summarized into six categories related to bone health: 1) Screening; 2) Risk Factors for Developing Low BMD; 3) Initial Assessment of Bone Health; 4) Diagnosis of Low BMD; 5) Subsequent Assessment of Bone Health; and 6) Management. These recommendations were then used to develop a draft management algorithm. The draft algorithm was reviewed by expert endocrinologists (AV and FM) and then refined following stakeholder feedback from gynaecologists, general practitioners and endocrinologists (n = 9) to achieve the final version (Fig. 2)

3. Results

Our search identified 145 records, 16 of which met our inclusion criteria (Fig. 1) and characteristics of included CPGs are presented in Table 1.

3.1. Methodological quality of CPGs

AGREE II scoring for each domain and final assessment of overall quality of the included CPGs is summarised in Table 2. The inter-rater reliability using the intraclass correlation coefficient values ranged from 0.71 (good) to 0.95 (very good). In eight instances the ICC was < 0.70, thus domain scores were re-discussed by reviewers to achieve greater concordance and ICC scores re-calculated.

High-quality CPGs were those developed by the National Institute for Health and Care Excellence (NICE) [22], European Society of Human Reproduction and Embryology (ESHRE) [1], Scottish Intercollegiate Guidelines Network (SIGN) [23] and The Endocrine Society [24], with mean total scores of 96%, 93%, 91% and 82% respectively. The NICE guideline ranked the highest with scores $\geq 88\%$ in all six domains. Eight average quality CPGs were identified (score range 56–74%) and four low quality (score range 40–58%). According to overall quality, four CPGs were considered “recommended”, eight “recommended with modification” and four “not recommended”.

Highest mean scores were obtained for Domain 1 (Scope and Purpose) and Domain 4 (Clarity of Presentation) at 85% (range 68–100%) and 87% (range 58–100%) respectively. NICE [22], ESHRE [1] and Endocrine Society [24] CPGs achieved maximum scores for Domain 1 and ESHRE [1] and The Endocrine Society [24] for Domain 4. The lowest mean score (44%; range 22–96%) was observed for Domain 5 (Applicability). A mean score of 58% was observed for Domain 2 (Stakeholder Involvement); the SIGN [23] (97%) and ACOG [25] (25%) being the highest and lowest scoring CPGs respectively. Domain 3 (Rigor of Development) was similar to Domain 2 with a mean score of 57% (range 30–99%) and the NICE CPG [22] was the highest scoring guideline. A mean score of 70% (range 15–98%) was observed for Domain 6 (Editorial Independence), with ESHRE [1] guidelines scoring the highest.

Table 1
Characteristics of guidelines included in analysis.

Title of Guideline	Year of publication	Country of origin	Organisation
Menopause [25]	2015	UK	National Institute for Health and Care Excellence (NICE)
Management of women with premature ovarian insufficiency [3]	2015	European	European Society of Human Reproduction and Embryology (ESHRE)
Long term follow up of survivors of childhood cancer – a national clinical guideline [26]	2013	Scotland	Scottish Intercollegiate Guidelines Network (SIGN)
Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline [27]	2015	Multinational	The Endocrine Society
Managing Menopause [37]	2014	Canada	The Society of Obstetricians and Gynaecologists of Canada (SOGC)
The 2017 hormone therapy position statement of The North American Menopause Society [35]	2017	USA	The North American Menopause Society (NAMS)
2016 IMS Recommendations on women's midlife health and menopause hormone therapy [31]	2016	UK	International Menopause Society (IMS)
The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer [33]	2012	European	The European Society of Breast Cancer Specialists
Spanish consensus on premature menopause [34]	2015	Spain	Spanish Menopause Society, Spanish Fertility Society, Spanish Contraception Society, Spanish Medical-Oncologic Society
First international consensus guidelines for breast cancer in young women (BCY1) [36]	2014	European	European School of Oncology (ESO), European Society of Breast Specialists (EUSOMA).
The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency [29]	2017	UK	British Menopause Society (BMS)
The British Menopause Society & Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women [32]	2016	UK	British Menopause Society (BMS)
Cancer-associated bone disease [38]	2013	Multinational	International Osteoporosis Foundation (IOF) and National Osteoporosis Foundation 2013
EMAS position statement: The ten point guide to the integral management of menopausal health [30]	2015	European	European Menopause and Andropause Society (EMAS)
Guidelines for menopausal hormone therapy: Recommendations of the Polish Menopause and Andropause Society – state of knowledge as of December 2013 [39]	2014	Poland	Polish Menopause and Andropause Society
Committee Opinion No. 698: Hormone Therapy in Primary Ovarian Insufficiency (ACOG) [28]	2017	USA	The American College of Obstetricians and Gynecologists (ACOG)

3.2. Guideline content and algorithm development

Recommendations from the highest four scoring guidelines (NICE, ESHRE, SIGN, The Endocrine Society [1,22–24]) were summarised into six categories related to bone health: 1) Screening; 2) Risk Factors for Developing Low BMD; 3) Initial Assessment of Bone Health; 4) Diagnosis of Low BMD; 5) Subsequent Assessment of Bone Health; and 6) Management (Table 3).

Content of these four highest scoring CPGs varied regarding the scope of recommendations pertaining to bone health. The most comprehensive guideline was ESHRE [1] with recommendations in all six categories. Two of the CPGs focused only on the management of bone health and had no recommendations for the other categories [22,24]. The quality of evidence in the guideline recommendations ranged from low to moderate quality (Table 3). The highest quality of evidence was of moderate quality from the ESHRE [1] guideline pertaining to “Initial Assessment of Bone Health” and “Management”.

Only the ESHRE [1] CPG had recommendations for “Screening” suggesting that assessment of BMD should be considered in all women at POI diagnosis.

Two CPGs had comments regarding “Risk Factors” in women with POI for developing low BMD. ESHRE [1] had discussion-based comments with no firm recommendation or grading of evidence, whereas the SIGN [23] CPG had recommendations from case reports/series (level 3 evidence) specific only to childhood cancer survivors (Table 3).

Regarding “Initial Assessment of Bone Health”, the ESHRE [1] CPG suggested assessment of BMD with Dual-Energy X-ray Absorptiometry (DXA) at diagnosis in all women with POI based on moderate quality evidence, whereas the SIGN [23] guideline specific to survivors of childhood cancer suggested BMD assessment 2 years following

cessation of cancer treatment. The other guidelines had no recommendations.

There was a paucity of evidence pertaining to the diagnosis of low BMD with no clear guidance from any CPG regarding the best way to define this.

“Subsequent Assessment of Bone Health” were only included in the ESHRE [3] and SIGN [23] CPGs. Based on low quality evidence, these CPGs suggested repeat assessment of BMD in non-childhood cancer survivors within 5 years following treatment initiation.

The “Management” category was the most comprehensive with similar recommendations from all four CPGs, which included commencing oestrogen replacement, if no contraindications, at diagnosis until at least the time of usual menopause.

Feedback for the algorithm was completed by 9 stakeholders (2 gynaecologists, 4 general practitioners, 3 endocrinologists) with minor refinements incorporated to produce the final version. Evaluations for the content regarding all sections of the algorithm ranged from ‘very good’ to ‘excellent’. All clinicians reported that the algorithm was helpful and they would use it if freely available.

4. Discussion

Our systematic search and AGREE II appraisal of CPGs related to POI and bone health indicates variability in quality domains between guidelines. Of the 16 CPGs evaluated, only four were assessed as high-quality and recommended by reviewers. Analysis of CPG content revealed variability and a paucity of high-quality evidence to guide management. Despite these limitations, a management algorithm to assist clinicians in the management of bone health in POI was developed and refined.

Table 2
Domain scores and overall assessment of Premature Ovarian Insufficiency and osteoporosis guidelines using AGREE II instrument.

Guideline title/Organisation	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigour of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence	Total score Mean (SD) (%)	Overall quality	Whether to recommend
Menopause: diagnosis and management (NICE) ²⁵	100%	96%	99%	99%	96%	88%	96 (5)	High	Recommended
Management of women with premature ovarian insufficiency (ESHRE) ³	100%	96%	93%	100%	74%	98%	93 (10)	High	Recommended
Long term follow up of survivors of childhood cancer (SIGN) ²⁶	99%	97%	92%	97%	88%	73%	91 (10)	High	Recommended
Treatment of Symptoms of the Menopause (The Endocrine Society) ²⁷	100%	61%	82%	100%	51%	96%	82 (21)	High	Recommended
Managing Menopause (SOGC) ³⁷	99%	65%	78%	96%	49%	56%	74 (21)	Average	Recommended with modification
The 2017 hormone therapy position statement of NAMS ³⁵	88%	49%	68%	97%	42%	94%	73 (24)	Average	Recommended with modification
2016 Recommendations on women's midlife health and menopause hormone therapy ³¹	78%	67%	56%	88%	42%	83%	69 (18)	Average	Recommended with modification
The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer ³³	79%	60%	51%	88%	35%	65%	63 (19)	Average	Recommended with modification
Spanish consensus on premature menopause ³⁴	78%	43%	40%	75%	23%	90%	58 (26)	Average	Recommended with modification
First international consensus guidelines for breast cancer in young women (BCY1) (ESO, EUSOMA) ³⁶	79%	46%	49%	81%	25%	67%	58 (22)	Average	Recommended with modification
The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency ²⁹	85%	31%	30%	83%	28%	88%	57 (30)	Average	Recommended with modification
The British Menopause Society & Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women ³²	68%	36%	35%	82%	34%	81%	56 (23)	Average	Recommended with modification
Cancer-associated bone disease (IOF) ³⁸	81%	44%	44%	83%	35%	58%	58(20)	Low	Not recommended
The ten point guide to the integral management of menopausal health (EMAS) ³⁰	79%	57%	30%	58%	28%	88%	57 (25)	Low	Not recommended
Guidelines for menopausal hormone therapy: Recommendations of the Polish Menopause and Andropause Society ³⁹	82%	49%	36%	76%	35%	13%	48(27)	Low	Not recommended
Committee Opinion No. 698: Hormone Therapy in Primary Ovarian Insufficiency (ACOG) ²⁸	68%	25%	31%	82%	22%	15%	40(28)	Low	Not recommended
Mean (SD) (%)	85 (11)	58 (22)	57 (25)	87 (11)	44 (23)	70 (26)			

Table 3
Summary of recommendations from highest scoring CPGs for assessment and management of bone health in women with POI.
Title of guideline

Menopause: diagnosis and management (NICE) ²⁵	Screening	Risk factors (RF) in women with POI for developing low BMD	Initial assessment of bone health	Diagnosis of low bone mineral density	Subsequent assessment of bone health	Management
	No recommendation.	No details.	No recommendation.	No recommendation.	No recommendation.	1. Offer sex steroid replacement - HRT or OCP (combined oral contraceptives) unless contraindicated. - Both HRT and OCP offer bone protection. - If contraindications to HRT/OCP give women advice on bone, CV health and symptom management. (low-very low quality of evidence) 2. Consider referring women with POI to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition. (Low-very low quality of evidence)
Management of women with premature ovarian insufficiency (ESHRE)³	1. Measurement of BMD at initial diagnosis of POI should be considered for all women. (C) - Initial assessment of bone health may include DXA scan to provide a baseline measurement.	<i>Included as a comment but no recommendation/grading:</i> Factors associated with low BMD: - Primary amenorrhoea. - Longer duration of POI - > 1 yr delay in diagnosis. - Age < 20 years at onset of irregular menses. - Low body mass index (BMI). - Low serum vitamin D. - Low dietary calcium intake. - Lack of exercise. - Non-compliance with oestrogen replacement	1. Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially where there are additional risk factors. (C) - If the duration of POI is short and oestrogen therapy has been initiated it is unclear whether DXA should be done in all women. - If long duration oestrogen deficiency or other RF (history of low impact fractures) should have baseline DXA assessment.	<i>Included as a comment but no recommendation/grading:</i> 1. BMD > 2.5 standard deviations below peak BMD for the appropriate reference group (i.e. young women from the same population).	1. If BMD is normal on initial DXA and adequate systemic oestrogen replacement is commenced the value of repeated DXA scan is low. (GPP) 2. If a diagnosis of low BMD is made and oestrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years. (GPP) - A decrease in BMD should prompt review of oestrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate. (GPP)	1. Women should maintain a healthy lifestyle to optimise bone health involving weight-bearing exercise, avoidance of smoking and maintenance of normal body weight. (GPP) 2. A balanced diet containing the recommended intake of calcium and vitamin D is recommended. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake and may be of value in women with low BMD. (C) 3. Oestrogen replacement is recommended to maintain bone health and prevent osteoporosis and it is plausible that it will reduce the risk of fracture. (C) - The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable. (C) - 17 β -oestradiol is preferred to ethinylestradiol or conjugated equine oestrogens for oestrogen replacement. (C) - Progestogen should be given in combination with oestrogen therapy to protect the endometrium in women with an intact uterus. (B) - Whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment. (GPP) 4. Consider patient preference for route and method of administration of each component of HRT when prescribing, as well as contraceptive needs. (GPP) 5. Once established on therapy, women with POI on HRT should have a clinical review annually, paying particular attention to compliance. (GPP) 6. HRT should be continued until at least the age of natural menopause to minimise control future cardiovascular and cognitive risk. (C) 7. Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. (C)

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Table 3 (continued)

Title of guideline	Screening	Risk factors (RF) in women with POI for developing low BMD	Initial assessment of bone health	Diagnosis of low bone mineral density	Subsequent assessment of bone health	Management
Long term follow up of survivors of childhood cancer (SIGN)²⁶	No recommendation.	RF associated with low BMD in childhood cancer survivors with hypogonadism: (3) 1. Hypogonadism AND hypothyroidism AND growth hormone deficiency. 2. Bone marrow transplant. 3. Treatment with; chemotherapy or glucocorticoids (higher cumulative dose increases risk). 4. Cranial irradiation. 5. Genetic polymorphisms in certain receptor of corticotrophin-releasing hormone receptor 1 gene and vitamin D receptor gene. 6. Caucasian ethnicity. 8. Physical inactivity. 9. Poor nutrition intake and Vitamin D.	1. Childhood cancer survivors whose treatment puts them at risk of endocrine dysfunction should have a baseline BMD at around 2 years after completion of treatment. (D)	1. When interpreting results of BMD should consider whether a patient's final height is compromised and the possibility of pubertal delay. (✓)	1. For survivors of childhood cancer repeating bone density in patients with results in normal range is not needed unless there is a clinical change in situation. (✓)	For survivors of childhood cancer: 1. No evidence on lifestyle modification improving BMD in these patients. (3) 2. Are at risk of hypogonadism and, in the absence of contraindications, sex steroid replacement therapy should be optimised. (3) 3. Endocrine evaluation is recommended for childhood cancer survivors who have a significant reduction in bone mineral density and/or recurrent fractures. (✓)
Treatment of Symptoms of the Menopause (The Endocrine Society)²⁷	No recommendation	No details	No recommendation	No recommendation	No recommendation	1. For young women with POI, without contraindications, suggest taking menopausal hormone therapy (MHT) until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2/XXOO) 2. For younger women with surgical menopause or those with POI who are accustomed to higher baseline endogenous oestradial levels, clinicians often prescribe higher starting doses of oestrogen therapy and then slowly lower the dose as tolerated. - When women with premature menopause approach the age of natural menopause, reasonable to reassess and taper dose of MHT.
Endocrine Society Clinical Practice Guidelines	Grades of recommendation 1 Strong recommendation 2 Weak recommendation	Level of evidence XXXX High-quality evidence XXXX Moderate-quality evidence XOX Low-quality evidence XOO Very low quality evidence O				
Long term follow up of survivors of childhood cancer (SIGN)	A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results B A body of evidence including studies rated as 2+*, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ E Recommended best practice based on the clinical experience of the guideline development group	1++ 1+ 1- 2++ 2+ 2- 3 4	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias Meta-analyses, systematic reviews, or RCTs with a high risk of bias High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal Non-analytic studies. E.g. case reports, case series Expert opinion			
NICE 2015	No specific grading system provided. Evidence was reviewed and the quality was described in detail for each question posed to be answered in the guideline					
ESHRE	A Meta-analysis, systematic review or multiple randomized controlled trials (RCTs) (high quality) B Meta-analysis, systematic review or multiple RCTs (moderate quality) C Single RCT, large non-randomized trial, case-control or cohort studies (high quality) D Single RCT, large non-randomized trial, case-control or cohort studies (moderate quality) E Non-analytic studies, case reports or case series (high or moderate quality) GPP Expert opinion					

The finding of “Clarity of Presentation” and “Scope and Purpose” as the highest scoring domains is comparable to other studies using the AGREE II instrument to evaluate guidelines related to a variety of conditions [39–41]. A recent systematic review assessing the factors associated with the quality of 421 CPGs related to the management of common diseases in primary care using the AGREE II instrument, similarly found these two domains to have the highest mean scores [42]. “Applicability” was the lowest scoring domain in our and other studies [40–42]. “Applicability” relates to the ability of the CPG to describe barriers to application and to give advice as to how the recommendations can be put into practice and monitored [38]. The low score in this domain may reflect greater resource investment into development than application and an under appreciation of the importance of CPG implementation and outcome monitoring [42,43]. Effective implementation programs of CPGs with primary treating clinicians have been shown to improve treatment targets [44], whilst CPGs with low applicability can limit compliance with the proposed recommendations [42]. The only guideline, which suggested barriers to implementation was the NICE guideline [22]. A high score in the domain “Rigor of development” indicates sound evidence-based guideline development and minimum bias. Systematic reviews reporting guideline appraisals with AGREE II found “Rigor of development” to have the strongest influence on overall guideline quality [45,46]. This is demonstrated in our study with the ranking of the highest to lower quality CPGs reflecting their scores for this domain.

“Editorial independence” was the third highest scoring domain in our study contrasting with other studies where it was the lowest scoring [39,41]. This was reassuring given that conflicts of interest among authors of guidelines may affect the quality of recommendations [39,41].

Knowledge gaps related to bone health management in POI were evident in the summary of CPG recommendations. Moderate quality evidence suggests that assessment of BMD with DXA scan should be considered for all women diagnosed with POI. However, only 35.9% of women with POI attending outpatient clinics at a UK teaching hospital had their BMD measured after diagnosis [47]. This may reflect poor implementation, consistent with the low “Applicability” scores in most CPGs.

Identification of risk factors for developing low BMD in women with POI are derived from observational studies with methodological limitations and the CPGs reflect this uncertainty [23]. Risk factors for low BMD in women with POI vary depending on aetiology. Identified risk factors for low BMD (Z score < -2) in women with spontaneous normal karyotype POI included: age < 20 years at onset of irregular menses, > 1 year delay in diagnosis, low serum vitamin D concentrations, low dietary calcium, non-compliance with oestrogen replacement and lack of exercise [9]. In contrast, women with Turner Syndrome have additional contributors to bone loss, skeletal fragility and falls risk; including genetic, hearing loss, coeliac disease and visuo-spatial abnormalities [48]. Women with breast cancer and iatrogenic POI have the additional risk factor of aromatase inhibitor therapy [49].

Diagnosis of low BMD and osteoporosis in young adults is challenging [8]. None of the CPGs provided specific recommendations on how to diagnose low BMD in POI. The use of DXA-derived BMD T-score to diagnose osteoporosis can generally not be used until peak bone mass has been achieved [8]. Additionally, areal BMD can be underestimated in individuals with short stature such as women with Turner Syndrome [1,9]. The 2019 International Society for Clinical Densitometry position statement recommend that Z-scores < -2 be used to define low bone mass in women before menopause; however, it does not specifically refer to women with premature menopause/POI [50]. An International Osteoporosis Foundation review of osteoporosis in young adults proposes that Z score < -2 be used to define low bone mass in young adult (pre-menopausal women); however, maintaining the use of T-score < -2.5 to diagnose osteoporosis in young adults suffering from chronic disorders known to affect bone metabolism [8]. Fracture risk

assessment tools, such as FRAX, are not validated for women under age 40 years.

Management of bone health was addressed in the four highest scoring guidelines; however, supporting evidence was predominately moderate to low-quality. Non-pharmacological management recommendations were only reported in the ESHRE CPG and were extrapolated from evidence related to lifestyle modification and fracture risk in postmenopausal women [1]. The SIGN CPG identified an observational study of childhood cancer survivors which indicated that BMD is improved by exercise [23]. Hormone replacement therapy (HRT) was recommended by all four highest scoring guidelines. Interestingly the highest scoring guideline, NICE, had recommendations in no other category apart from management of bone health in women with POI, outlining the limitations of the AGREE II instrument and the inability of this tool to evaluate content [22]. A recent meta-analysis, including both observational and randomised controlled studies of women with different causes of POI, concluded that HRT increased lumbar spine BMD with inconclusive evidence regarding hip BMD or fractures and variable response depending on the cause of POI [51]. A meta-analysis assessing HRT in women with Turner syndrome indicated increased lumbar spine BMD with oestradiol containing HRT but not ethinyl-oestradiol or conjugated oestrogens [52]. The general consensus from the CPGs was that women diagnosed with POI should commence oestrogen replacement at diagnosis, with oestradiol preparations potentially having more favourable effects on BMD, and should be continued at least until the age of natural menopause [1,22–24].

The ESHRE CPG recommends that other pharmacological interventions, including bisphosphonates should be considered with advice from an osteoporosis specialist and particular caution applies to women desiring pregnancy [1]. A small study (n = 60) of women with POI secondary to chemotherapy for allogeneic stem cell transplant indicated that bisphosphonate therapy for 12 months increased lumbar spine BMD whereas HRT did not [53].

Only two guidelines provided recommendations for subsequent assessment of bone health based on clinical experience and expert opinion only, reiterating the lack of evidence in this field [1,23].

A management algorithm was developed based on the recommendations of the four highest scoring guidelines, with refinement by experts in the field as well as potential end-users. Algorithm recommendations related to screening and risk assessment, initial and subsequent assessment of bone health and diagnosis of low BMD were largely formulated from two out of the four top scoring guidelines [1,22], mainly from the ESHRE CPG, as the remaining CPGs did not offer recommendations in these areas. This proposed algorithm is limited by the gaps and quality of evidence of the four guidelines on which it is based. Women with POI report osteoporosis as one of the most feared consequences of POI [54,55]. This highlights the urgent need for research directed at overcoming the identified knowledge gaps to facilitate optimal bone health.

Study strengths included use of (i) an extensive search strategy, (ii) a validated tool (AGREE II) to grade CPG methodological quality, (iii) multiple trained appraisers scored the CPGs, (iv) high inter-observer agreement and (v) clinician input to refine the algorithm. Our study was limited in that (i) only English language CPGs were included, and (ii) the AGREE II instrument, robust to assess CPG methodological quality, does not evaluate content or the degree of consistency between CPG recommendations and the reported evidence.

5. Conclusion

Most CPGs regarding bone health in women with POI are of average to poor-quality with significant limitations in most AGREE II domains. The AGREE II instrument could assist CPG development to optimize quality and also when deciding which CPGs to implement in clinical practice. The limited evidence underpinning recommendations

indicates the need for further research. From the available evidence and with stakeholder engagement, we have devised a management algorithm to aid clinicians in the management of bone health in women with POI.

Contributors

Velislava Kiriakova participated in the data analysis and interpretation, and the drafting and revision of the manuscript.

Shamil D Cooray participated in the study design, data acquisition and analysis, and the drafting and revision of the manuscript.

Ladan Yeganeh participated in the data analysis, and the drafting and revision of the manuscript.

Gowri Somarajah participated in data acquisition and revision of the manuscript.

Frances Milat participated in all aspects of preparation of the manuscript.

Amanda J Vincent participated in all aspects of preparation of the manuscript.

All authors saw and approved the final version of the manuscript.

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Ethical statement

This study did not involve experimentation with human subjects and therefore informed consent and ethical approval was not required.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of Competing Interest

Amanda J Vincent serves on the editorial board of the journal *Climacteric*, which published one of the clinical practice guidelines in the study.

All other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.maturitas.2019.07.021>.

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