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Subjective cognitive changes following premenopausal risk-reducing bilateral salpingo-oophorectomy

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ABSTRACT

Objective: Women at high risk of ovarian cancer are commonly advised to undergo risk-reducing bilateral salpingo-oophorectomy (BSO) prior to natural menopause. Cognitive symptoms during natural menopause transition are frequently reported; however, very few studies have examined cognitive changes following surgical menopause. To address this gap, we explored the cognitive experiences of women within 24 months post BSO.

Methods: This observational cross-sectional sub-study is part of a larger project, the Early Menopause and Cognition Study (EM-COG). We investigated perceived cognitive experiences in Australian women ($n = 16$) who underwent risk-reducing BSO using qualitative interviews. Thematic analysis was undertaken to identify key themes.

Results: Fifteen out of 16 participants (93.75%) reported changes to cognition within 24 months post BSO. The key cognitive symptoms reported were brain fog, memory and retrieval difficulties, slower processing speed as well as attention difficulties. Five participants (31.3%) experienced negative mood symptoms post BSO.

Conclusion: Findings from this study suggest that women experience subjective cognitive changes within 24 months post BSO. This period could be a vulnerable time for women's cognitive health. While these findings need to be confirmed by a large prospective study, our research indicates that psychoeducation and awareness will be helpful in managing cognitive symptoms after surgical menopause.

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Surgical menopause; subjective cognitive experiences; bilateral salpingo-oophorectomy; brain fog; memory

Introduction

Surgical menopause occurs following bilateral salpingo-oophorectomy (BSO) in young women who have not undergone natural menopause. In contrast to the changes in ovarian sex steroid hormone production associated with natural menopause [1–3], surgical menopause resulting from BSO is associated with an abrupt decline in gonadal hormone production [4,5]. Women who are at high risk of ovarian cancer, for example those with a *BRCA1/2* pathogenic variant, are commonly advised to undergo risk-reducing BSO prior to natural menopause [6,7].

Previous research in this area suggests that women who undergo surgical menopause experience similar symptoms to natural menopause in terms of vasomotor symptoms [8], sleep disturbance [9] and an increased risk of clinically significant depressive and anxiety symptoms [10]. Cognitive symptoms, often described as 'brain fog', have been described during natural menopause [11,12], with up to 60% of women describing a subjective cognitive decline during the natural menopause transition [13] and objective testing indicating a subtle decline predominantly in the domains of verbal memory and attention [14–17]. A limited number of studies have examined cognitive symptoms in the context of surgical menopause, and results have suggested perceived cognitive impairments that develop within 6 months post BSO [18] as well as reduced cognitive performances following surgical menopause [13].

Most studies examining the cognitive effects of surgical menopause have focused on the long-term effects [19–22]. A systematic review reported that early, surgical menopause induced by BSO in women younger than 45 years was associated with an increased risk of dementia and later life cognitive decline [23]. Similarly, a subsequent case–control study of 2732 women reported that surgical menopause in women younger than 46 years was associated with lower cognitive scores on measures of global cognition, attention and

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executive functions, as well as an increased risk of mild cognitive impairment later in life [24].

To develop an understanding of women's experiences of cognitive symptoms following surgical menopause, the primary aim of this study was to investigate the subjective cognitive experiences of women within 24 months post BSO using qualitative interviewing.

Methods

Study design

This observational cross-sectional study was part of a larger project: the Early Menopause and Cognition Study (EM-COG). The broader project aims to provide a prospective assessment of cognition pre and post BSO. This sub-study utilized a thematic analysis approach [25] to explore cognitive experiences within 24 months post BSO in women who were younger than 45 years and at high risk of ovarian cancer due to high-risk cancer genetic predisposition. This approach was chosen to capture perspectives of human psychology that are not necessarily objective [26]. Moreover, using semi-structured interviews enabled descriptive exploration and reflection of cognition post BSO.

Recruitment and participants

Ethics approval was obtained from the Alfred Ethics Committee (project number 759/20) and Monash University Human Research Ethics Committee (project number 29324). Recruitment occurred through social media advertisements on social media as well through recruitment from familial cancer genetics clinics in Melbourne, Australia, between March 2021 and August 2022 as part of 'EM-COG'. Women were included if they were: aged between 18 and 49 years; were considered to be at high risk of ovarian cancer (e.g. women with a *BRCA1/2* pathogenic variant and/or high familial risk); and had risk-reducing BSO prior to the onset of natural menopause within the previous 24 months. The age range of participants between 18 and 49 years, combined with screening questions about menstrual cycle regularity, was maintained to ensure that women had not reached menopause at the time of BSO. The exclusion criteria included a severe mental illness or neurological condition that may impact cognition (e.g. severe head injury, central nervous system condition or psychosis) [27] and non-English-speaking participants.

Procedures

Eligible participants were invited to participate in the study via videoconferencing or in person at HER Centre Australia, Monash University, Melbourne, Australia. Informed consent was electronically provided through the REDCap (Research Electronic Data Capture) electronic data capture tool hosted and managed by Helix (Monash University) [28,29]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for data integration and interoperability with external sources.

Demographic information was collected on age, medication and the use of hormone therapy. The Mini International Neuropsychiatric Interview (MINI) was used to screen participants for the presence of any psychiatric conditions which could affect their performance in the interviews [30,31]. Two self-report measures were used to measure vasomotor symptoms. The Hot Flush Rating Scale (HFRS) was used to measure the presence and frequency of vasomotor symptoms [32], and the Hot Flash Related Daily Interference Scale (HFRDIS), a 10-item questionnaire, measured the impact of hot flushes on daily activities and quality of life in the past week on a scale from 0 (does not interfere) to 10 (completely interfere) [33]. The Insomnia Severity Index was used to quantify self-reported insomnia symptoms [34]. The interviews were conducted by authors A.R., C.G. and E.H.X.T., and took approximately 15–25 min depending on participants' responses and the amount of probing which was required. Nine open-ended questions were developed, using previous literature as a guide, to explore whether cognitive symptoms were observed post BSO (see Table 1). All interviews were recorded and transcribed verbatim following the interview for analysis.

Analyses

Thematic analysis followed the six-step procedure from Braun and Clarke [25,35] to examine the common themes derived from qualitative interviews. After interviews were transcribed verbatim, transcripts were re-read. Annotation of transcripts occurred using the research questions as a guide to identify the key phrases and responses of relevance. Following this, codes (representative of raw data) were generated to encapsulate these key phrases and responses. These were categorized into broader themes which were generated using patterns and trends from previous literature. Subsequently, themes were developed based on new topics which emerged as areas of research interest. After refinement, theme names were established from key words used by participants. Initial analysis and coding were completed by the first author (A.R.), and checked by authors E.H.X.T. and C.G. Analysis was

Table 1. Questions asked during the interview.

Question
Tell me about your experience of surgical menopause?
Have you noticed any changes to your thinking skills following the surgery?
Some people talk about brain fog/mental fatigue, is that something you have experienced?
Can you provide examples of times when you have experienced brain fog?
To what extent does your …. affect your quality of life?
What sorts of coping strategies do you use?
Was menopausal hormone therapy used after surgical removal of ovaries, and if so, did you notice any changes in your experience of mental fatigue or brain fog? Did menopausal hormone therapy have an improvement or change?
We have talked a lot about the negative things, have you noticed any positive changes in your thinking skills after removal of ovaries?

reviewed and verified by all authors using direct quotes from the data in order to ensure that the study findings were rigorous and credible [36].

Results

Demographic and clinical characteristics

Eighty participants responded to advertisements or were referred into the study and screened. Of these, 64 participants were excluded due to either living outside Australia ($n=2$), current or previous chemotherapy ($n=6$), already perimenopausal ($n=2$), no BSO within the past 24 months ($n=25$) or loss to follow up/no longer interested ($n=29$). Sixteen participants completed a qualitative interview (15 via videoconferencing and one in-person). The average time post BSO was 7.65 months (standard deviation [SD] = 8.25 months, range = 8.8–28.5 months) and all women had a *BRCA1/2* pathogenic variant (*BRCA1*, $n=7$; *BRCA2*, $n=9$). Mean age at the time of interview was 41.83 years (SD = 3.99 years range = 36–49 years). Seven of the 16 participants had a postgraduate qualification, three had a bachelor degree, four had vocational training and two had a high school diploma. Fifteen participants were Caucasian and one was of Persian/Indian descent. Twelve out of 16 participants have been taking menopausal hormone therapy (MHT; estrogen and/or progesterone) since their BSO (average duration of MHT use was 7.65 months, SD = 8.25 months). The average daily frequency of hot flushes was one per day (range 0–6) and the average interference score on the HFRDIS was 0.9 (SD = 1.4). The mean score on the Insomnia Severity Index was 10.31 (SD = 6.54), falling into the subthreshold score range (the range of scores across participants was 2–23).

Participants' experiences of cognitive changes

Participants' experiences of cognitive changes were identified and extracted from the interviews. The main themes were 'brain fog', memory and word retrieval, as well as slower speed of processing and attention difficulties. Of the 16 participants, 15 reported changes to their cognition post BSO.

Participants' experiences of brain fog

'Brain fog' was reported by 10 of the 16 participants. The severity of brain fog varied with each participant, although similar explanations of brain fog were reported. While some women described it as 'frustrating' and 'getting worse', others said it was apparent 'now and again'. Brain fog in itself was described by women as feeling 'bit heavy or clouded', 'can't get past the haze', 'fuzzy', 'intense' or in 'some kind of lost forward feeling'. Women connected 'brain fog' to different situations in the context of work or completing tasks that required attention to detail as well as in social settings when interacting with others.

One participant reflected: 'I thought I had a virus … I didn't know what was going on … I realized after a while that it was probably that brain fog' (Participant 11). Two of the participants also noted that their experience of brain fog had increased over time, stating that the 'brain fog is getting worse' and 'I find that it's getting worse sometimes'.

Participants' experiences of memory

Eight out of the 16 women described negative changes to memory post BSO. Three women described experiences that were explicitly related to short-term memory: 'I think it all goes back to that short-term memory … There's definitely been memory loss.' No participants reported long-term memory changes, but participants described the notion of losing their intentions or train of thought: 'I'm midway through something and … I can't remember what I was doing or why I was doing it' (Participant 5); 'I was more forgetful. I would go into the kitchen to get something … And … I don't know what I was going to get' (Participant 6); and 'You know, I go to do things, and then I've got no idea. Which … happens to everybody, but it's happening a lot more often to me' (Participant 7).

In relation to retrieval, five of the 16 participants highlighted word retrieval as a particular challenge. Three participants described similar experiences of being unable to retrieve words from memory in general situations: 'I'm talking and just mid-sentence, the only way I can describe [it] is almost like someone's put their hand in my head and just taking words out and I just have no clue what I was about to say. It's just completely gone' (Participant 9); and 'Even just little things, like I was trying to think of a song name that I knew very well and it just wouldn't come to me, and then about 2 h later, it just popped into my head' (Participant 14). In response, participants sought to develop new strategies to minimize the disruptions that of these retrieval difficulties: 'The only new [strategy] is probably just, rather than wanting to think of the word myself or use a different word, is to get other people to help me think of it' (Participant 3).

Participants' experiences of attention and speed of processing

Eight of the 16 participants reported themes related to slowed thinking or processing, with comments made such as '[my thinking skills] are probably slower. It's slow because it's tired because of the brain fog' (Participant 5); and 'Sometimes someone might ask me something, and it might take me a long time to answer because I've got to think about it' (Participant 8). Another participant explained that it is not related to fatigue: 'No, not tiredness. It's just trouble thinking' (Participant 6). Four participants reported changes to their attention in terms of reduced focus such as 'my attention span is all over the place' (Participant 5) and 'my attention span's a lot shorter than it normally would be' (Participant 7), or increased distractibility: '… really easily distracted on something completely different' (Participant 5).

Participants' perceptions about the role of menopausal hormone therapy

Twelve out of 16 participants were taking MHT (estrogen and/or progesterone), and of those participants 75% reported

brain fog and 58.3% reported memory problems. Of the four participants not taking MHT, three (75%) described negative changes to cognition and one participant reported that 'brain fog is getting worse'. All participants who were taking MHT commenced MHT at the time of their BSO, hence it was not possible for participants to comment on whether MHT was helping their cognition.

The impact of cognitive symptoms

The negative impact of cognitive changes on work was described by two participants: 'I don't feel like myself anymore. Because I used to be a … general manager … And I really didn't feel competent to do that anymore. I really just didn't know what hit me' (Participant 10); and 'I've lost a lot of confidence in my work …' (Participant 16).

Participants' experiences of mood changes

When broadly discussing their experiences of surgical menopause, five participants described negative mood changes in terms of their mood being less predictable – 'My mood is less predictable'; Participant 1 – as well as increased irritability: 'I feel like I'm getting a little bit cross at things that just really aren't worth it' (Participant 2); 'I think probably baseline irritability levels just sit slightly higher' (Participant 10); and '… definitely more irritable … probably my mood was a bit down' (Participant 12). One participant described alterations in how they were perceived by others as a result of their mood fluctuations: 'I definitely wasn't a nice person to be around' (Participant 11). In addition to these negative impacts on mood, 14 women described the reduced anxiety they are enjoying relating to the reduced risk of ovarian cancer post BSO: 'a little bit relieved … that risk is gone' (Participant 1); 'I feel better … very minimal chance that I'm going to get ovarian cancer' (Participant 3); and 'It's one less thing to worry about' (Participant 4).

Discussion

To our knowledge, this is the first qualitative study to investigate experiences of cognitive symptoms in women post BSO. The key cognitive symptoms reported in the current study were brain fog, memory and retrieval difficulties, and slower processing speed as well as attention difficulties. While the number of participants was not large, the observations and insights were consistent among the interviewed women. Moreover, these observations add to the limited literature examining cognitive symptoms in the context of surgical menopause [13,18,37].

All but one of the women reported some type of cognitive symptom post BSO. 'Brain fog' was reported by 63% of participants, although the way it was characterized varied. The term 'brain fog' has recently been defined in the context of natural menopause as a constellation of cognitive symptoms that broadly includes memory and attention difficulties [38].

Half of the women from the current study reported memory symptoms post BSO that were characterized as difficulties in working memory or short-term memory as well as retrieval difficulties (including word finding problems). One previous study measured verbal memory in a sample of 19 women pre and post BSO, and the results demonstrated a decline in verbal memory post BSO [39]. Natural menopause is also associated with a small decline in measures of immediate and delayed verbal recall, shown to be independent of normal age-related cognitive decline [40]. Slower speed of processing post BSO was described by half the women in this study. In relation to processing speed during natural menopause, some studies have reported that processing speed (when measured objectively with neuropsychological tests) transiently declined during the menopause transition (although performance scores remained in the normal range) and rebounded in postmenopause [40–42]. The participants in the current study also described reduced attention post BSO. Difficulties with attention, in the form of elevated scores on an attention deficit scale, have been reported in both surgical menopause and perimenopause groups, in relation to premenopausal women [43], and studies have reported there is an association between subjective reports of attention difficulties and objective testing on attention during natural menopause [44].

Negative mood changes were reported by five women in the current study. Previous research exploring depression post BSO is mixed [45]. A prospective controlled observational study (What Happens After Menopause [WHAM]) demonstrated that at 3 months post BSO the risk of clinically significant depressive symptoms doubled, and remained elevated at 12 months post BSO. The risk of anxiety symptoms tripled within 3 months post BSO but plateaued by 6 months [46]. In contrast, a large prospective cohort study of 25,288 nurses looking at the long-term associations between BSO and depression (ascertained by antidepressant prescription) did not report significantly higher rates of depression in women who had previously had a BSO compared to women who retained their ovaries. The natural menopause transition is described as a period for increased risk for the development of both depressive symptoms and major depressive episodes [45]. Hence, there is a need for more research to explore whether women are at an elevated risk of depression post BSO.

Other menopausal symptoms, such as disrupted sleep and vasomotor symptoms, may also contribute to, or exacerbate, the experience of brain fog [47]. The frequency of hot flushes in this small sample was, on average, one per day and the average impact was minimal. The average insomnia rating scale score was placed in the subthreshold range and while the range of responses included scores in the moderate and severe ranges, the capacity to analyze the impact of disrupted sleep and vasomotor symptoms on brain fog was not possible in this small sample and is an area for future research.

The therapeutic effects of MHT for mood and cognitive symptoms in natural menopause is currently unclear. Current guidelines do not recommend MHT as first-line treatment for either mood or cognitive symptoms during menopause

[38,48]. Twelve of the 16 women in the current study were taking a form of MHT. Given the potential for an increased risk of later life cognitive decline and dementia in women who have early surgical menopause [23], and the potential role for MHT in reducing this risk [49], this is an important area worthy of future research. The limited research examining the impact of hormone therapy on cognition within the first 6 months post BSO has reported no association between use of hormone therapy and cognition [13], a positive effect of hormone therapy on working memory [37] as well as declines in subjective memory associated with hormone therapy [18].

Much of the theoretical evidence underpinning the idea that MHT may benefit cognition has come from animal studies that have demonstrated that estradiol plays a role in increasing synaptic density, plasticity and neurogenesis in the hippocampus and the prefrontal cortex [50–54]. Use of ovariectomized animals and estrogen receptor (ER) knockout models has demonstrated that the removal of estrogen is implicated in learning and memory difficulties, and these difficulties can be reversed with estradiol replacement [55]. Research in women post BSO is limited, but one prospective study assessed women pre and post BSO, alongside a control group of women, and reported that, at 6 months post BSO, the BSO group demonstrated a cognitive decline relative to the control group. Within the BSO group, women who had a greater drop in estradiol levels had a greater decline in cognition [13]. Taken together, these findings suggest that estradiol may play a neuroprotective role, aiding cognition in the short and long term, and this provides a rationale for further research into the potential benefits for MHT in women post BSO.

Limitations and areas for future research

The generalizability of this study is restricted by the small sample. The sample characteristics included predominantly Caucasian women with high levels of education and most were taking a form of MHT. The experience of menopause may vary between women with different cultural and ethnic backgrounds [56,57]. High levels of education are thought to be associated with better cognitive performance, a greater cognitive reserve as well as potentially providing a form of neuroprotection [58]. The questions asked in this study included leading questions, which may have also prompted women to report symptoms that may have not been particularly bothersome. The findings from this study highlight the need for prospective research involving neuropsychological testing pre and post BSO, as well as a control group of similar aged participants, which we plan to address in a separate study. Previous research has indicated that women preparing for risk-reducing BSO were concerned about the lack of information provided on the potential post-surgical impacts on cognition [59]. Taken together with the current findings, future research should examine the potential benefits of psychoeducation as well as strategies to help manage any cognitive symptoms and how to best implement these in clinics where these women are seen.

Conclusion

Cognitive changes are reported in natural menopause, but not well studied in surgical menopause. This qualitative study revealed key themes including the experiences of brain fog, memory impairments and changes in thinking skills. While these findings remain preliminary, they suggest that women may experience cognitive symptoms within the first 2 years post BSO. These findings provide a strong rational for future prospective research to provide an evidence base for any cognitive changes and the need for more awareness in managing subjective cognitive changes in the context of surgical menopause.

Potential conflict of interest No potential conflict of interest was reported by the authors.

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