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Review article

Ageing perspective on cognitive outcomes from ancillary reproductive hormone adjustments

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ABSTRACT

In addition to primary reproductive functions, gonadal hormones play an important role in regulating neural mechanisms across the human lifespan. The ageing-related decline in their activity has been linked to cognitive impairments in otherwise healthy women, contributing to higher incidents of post-menopause dementia. Given the growing utility of gonadal steroids for birth control, as well as for compensatory treatment of menopause and oophorectomy symptoms, and adjuvant transgender therapy, their long-term effects on neural mechanisms warrant comprehensive assessment. In this article, we present an ageing perspective on the cognitive outcomes of contraceptive and ancillary medical use of gonadal hormones and discuss their effects on the risk of cognitive impairments and late-life dementia. Despite rising data supporting the ameliorative effects of reproductive hormones on cognitive facilities, their impact varies depending on study design and type of intervention, implying dynamic neuro-endocrine interactions with complex compensatory mechanisms. Elucidating differential effects of reproductive hormone adjustments on cognition is expected not only to shed light on important aspects of brain ageing and dementia but to facilitate their use in personalized medicine with better safety and therapeutic outcomes.

1. Introduction

Given the ageing global population, the rise in various types of dementias in late-life imposes a major challenge to society and public health [1,2]. Related with ageing decline in reproductive functions due to gonadal hormone fall-off has caused much interest as a potential risk factor for cognitive impairments, engendered by growing evidence of the improvement in higher brain mechanisms by hormone therapy [3–6]. In addition to classical endocrine effects on the brain produced by peripheral gonadal hormones, some are synthesized and released in the central nervous system, acting as potent neuro-steroids, modulating an array of neural mechanisms and

Abbreviations: HRT, hormone replacement therapy; ER-α, oestrogen α receptor; AD, Alzheimer's disease; PD, Parkinson's disease; GA, general anaesthesia; SA, spinal anaesthesia; MCSO, Mayo Clinic Cohort Study of Oophorectomy and Aging; GHT, gender-affirming hormone therapy; MMSE, Mini-Mental State Examination; SCD, subjective cognitive decline; BRFSS, Behavioural Risk Factor Surveillance System; TNB, *trans*-gender nonbinary; AFH, adjuvant female hormones.

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activities [7–10]. Like in peripheral tissue, the effects of gonadal hormones in the brain are mediated via three routes: (1) regulation of gene expression, through interactions with specific nuclear receptors, (2) activation of membrane receptors with modulation of associated signalling and cellular functions, and (3) control over the effects of neurotrophic factors and their action on neural processes [8,11–14]. Overall, gonadal hormones have revealed a rich repertoire of mechanisms for influencing synaptic plasticity, rearrangement and remodelling of neurotransmitter receptors, and regulating biochemical pathways implicated in cognition.

In support of their involvement in higher brain functions, substantial data suggest a positive correlation between hormone deficiency and cognitive downturn with associated dementia in late-life [15]. Reports imply that multiple neural processes and their impairments during ageing can be influenced by the declining level of gonadal hormones, while hormone replacement therapy (HRT) leads to protection and partial recovery [16–18]. In addition to the ageing-related decline in the activity of gonadal hormones, analysis of the expression of oestrogen receptors showed a significant reduction with remarkable changes in distribution within the ageing brain [19,20], implying complex alterations, which warrant further analysis in preclinical and clinical studies. There is ample evidence suggesting that hormonal adjustments can protect against the onset of dementia in post-menopausal women, with cognitive outcomes depending on the type of interventions and age at their commencement [21–23]. Nevertheless, considerable knowledge gaps and controversies remain as to how gonadal hormone therapy can prevent or slow down the post-menopausal decline in cognitive functions. Some researchers have speculated that there is a critical therapeutic window during menopause, characterized by abrupt hormonal decline or adjustments to oestrogen α receptor (ER-α) expression, when the application of hormone therapy yields most of the late-age cognitive benefits [24].

Female gonadal steroids (e.g., oestrogen and/or progesterone and their analogues) have been increasingly utilized over decades for birth control, as well as for compensatory adjustments against functional decline related to menopause (Fig. 1). More recently, the use of gonad hormone has been extended for oophorectomy-hysterectomy or gender realignment [25–28]. Inconsistent effects have been assigned to the paucity of the data, variations in study design, small sample size, differences in treatment duration and other factors. In this study, we revisit the long-term impact of the use of gonad hormones for reproduction control, HRT, hysterectomy and adjuvent trans-gender hormonal therapy on cognitive functions and the risk of late-life dementia (Fig. 1). We searched PubMed, Science Direct and Google using keywords and phrases: 'cognition; adjuvant female hormones; dementia; Alzheimer's disease; contraceptives; *trans*-gender alignment therapy', focusing our discussion mainly on primary research papers and clinical trial data since 2000. We review the major developments in the field and revisit outstanding questions and challenges, which not only confirm the emerging positive effects of gonadal hormones on the performance of aging brain but may facilitate the development of personalized and safe therapeutic interventions for countering cognitive decline and dementia in late-life.

2. Late-life cognitive outcomes of reproduction control with hormonal contraceptives

Given the widespread use of hormone-based contraceptive pills for birth control, their long-term cognitive impact is of major healthcare relevance. A prospective study assessed the impact of reproductive timeframe duration and parity with the use of contraceptives on the risk of cognitive impairment in women at a later age with natural menopause [29]. Individuals were functionally

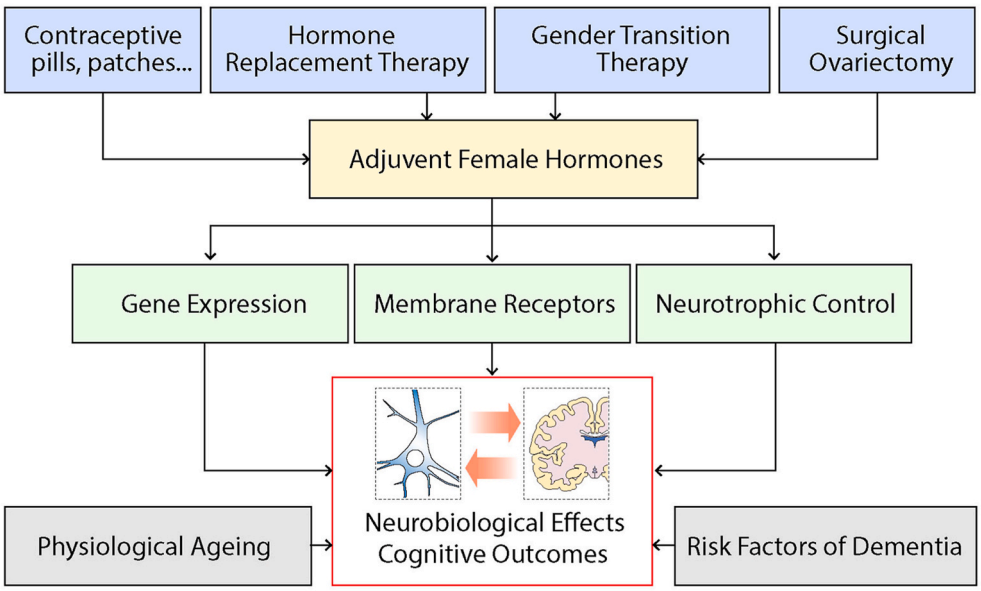

Fig. 1. Schematic representation of the hormonal adjustment approaches along with their action pathways. In combination with physiological ageing and effects of dementia risk factors, hormonal changes can affect neurobiological mechanisms leading to cognitive alterations. The effects of hormonal manipulations on cognitive facilities are discussed throughout this study.

assessed in multiple domains, including spatial orientation, immediate and delayed recall, attention, language, and visuospatial ability, with lower score ratings indicative of abnormal cognitive performance. An education-specific cut-off point was set to ensure the relative homogeneity of the cohort. Those found contraceptives eliciting late-age cognitive impairments were more senior, smokers, had low education levels, were not co-habiting or had been afflicted with chronic diseases [29]. Women with less than thirty-five reproductive years were at significantly higher risk of cognitive impairment compared to women with up to four more years of fertility. For every one-year increment in the age of the onset of complete menopause, a reduction in odds of cognitive impairment was noted. Protection against future dementia was elicited by oral contraceptive use over 5 years and longer, as compared to those who had never taken oral contraceptives [29].

Another study assessed a prospective population-based cohort for late-life dementia linked to reproductive function and contraceptive usage in middle-aged women [30]. Self-reported reproductive factors of this report included the use of oral contraceptives and the age of their initiation. Cox proportional hazard regression models indicated that shorter cumulative exposure to female hormones was associated with an elevated risk of dementia [30]. A cross-sectional analysis of females with positive or negative parental history of Alzheimer's disease (AD) identified significantly enhanced cognitive performance associated with hormonal contraceptive use in comparison with nonusers [31]. All subjects completed neuropsychological assessments including intelligence, word fluency, verbal learning and working memory. Comparability of the hormonal contraceptive ever users versus never users accounted for race, education, age, socioeconomic status, and depression [31]. Secondary analysis for differences in cognitive outcomes depending on the length of contraceptive use revealed that the overall performance increased as a function of hormonal use duration [31]. When adjusting for age, socioeconomic status, parity, and years of education, hormonal contraceptive use was found to be associated also with improved visuospatial ability, speed and flexibility performance [31]. The physiological basis for the emerging evidence and specific mechanisms of cognitive protection by the long-term use of contraceptive pills as well as effects after discontinuation remains to be elucidated. Nevertheless, major targets and functional processes have been identified, which have been implicated also in cognitive decline and pathology of neurodegenerative diseases involving β-amyloid production pathways, phosphorylation of tau protein, neuro-inflammation and glutamate cytotoxicity [32] (Fig. 2).

3. Late-life cognitive outcomes of hormone replacement therapy in post-menopausal women

Conflicting evidence has been recognised concerning whether HRT exposure offers protection or risk for dementia in post-menopausal women [33,34]. A formative randomised double-blind placebo-controlled primary prevention trial found that conjugated equine oestrogen plus medroxyprogesterone (progestin) increased overall dementia risk and cognitive decline in women who were sixty-five years or older [33]. A large observational study found that specifically for AD, a small increased risk was associated with more than five years of oestrogen-progestogen treatments and suggested that the risk of developing the disease increased by HRT [23]. This was supported by another large study of women living in Finland which found that those with AD used systemic hormone therapy more often than aged-matched healthy controls [35]. Note, the exclusive use of vaginal oestradiol did not affect the risk of the disease [35]. The elevated risk for AD was also noted in women taking oestradiol only or oestrogen-progestogen therapy for 10 years or more, whereas shorter use of hormone therapy was not associated with such risk [35]. Another study of the same cohort from Finland with a twenty-year follow-up reported that the use of systemic oestrogen and progestogen was associated with an increased risk of AD

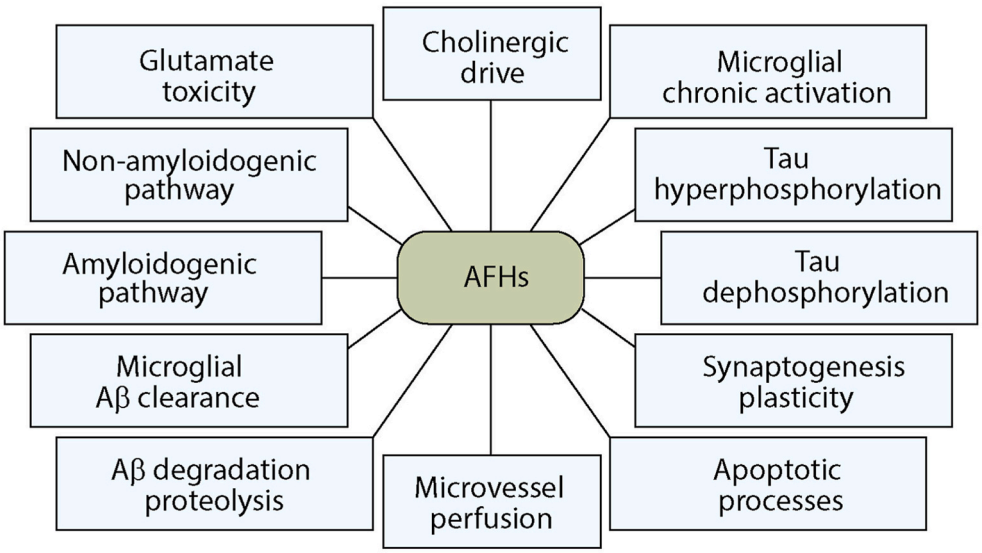

Fig. 2. Literature based schematic representation of the major targets and functional consequences of adjuvant female hormones (AFHs) therapy implicated in cognitive changes. As highlighted throughout this study, AFHs adjustments may lead to changes in brain mechanisms along with bidirectional alterations in cognitive functions.

but not after long-term use (>10 years) [36]. The authors concluded that their data did not provide evidence for a protective association between post-menopausal HRT use and AD or dementia, although a reduced AD risk was observed among those with long-term self-reported HRT [36,37].

A similar analysis of the relationship between menopausal HRT, AD and Parkinson's disease (PD) using a random effect model showed a significant association between HRT, AD, and all-cause dementia with hormone therapy [38]. The relationship between HRT and AD was found to be more pronounced in patients receiving the combined oestrogen-progestogen formulation. No association was found between HRT and PD [38]. In contrast, a meta-analysis found a decreased risk of dementia in similarly aged women taking only oestrogen as HRT but recognised the methodological limitations of most of the included studies [39]. The Kronos Early Estrogen Prevention Study (KEEPS), a randomized, multi-centred, double-blind, placebo-controlled, prospective trial compared oral conjugated equine estrogen to transdermal estradiol in women aged 42–58 years who are within 36 months of their final menstrual period [40]. All participants also availed to natural and cyclic progesterone. The KEEPS trial revealed that women receiving transdermal estradiol performed better on subjective memory tests than women receiving oral estrogen or placebo. Furthermore, these women experienced less cortical atrophy and were less likely to show amyloid accumulation in brain PET imaging [41]. Another case-control study reported that while the risk for AD increased in women younger than 60 years of age at HRT initiation with over ten years of exposure, the age at commencement of systemic hormone therapy was not a decisive determinant [35]. Others found a decreased risk of dementia for women younger than 80 years at diagnosis who had been taking oestrogen-only therapy for 10 years or more [23]. The focus then turned to younger postmenopausal women with a stratified analysis revealing the protective association of HRT against AD being age-dependent [34]. Findings revealed that oestrogen HRT protected the youngest age group but not the older groups from cognitive decline (50–63 years) [34]. There was no interaction between HRT use and education or race. Song et al. analysed the association between HRT, AD and PD [42]. The results showed that HRT decreased the risk of onset and/or development of AD and PD compared with the group not receiving HRT [42]. While recognising that the marginal age-dependence of hormonal effects on cognition could be down to chance, a 'critical window' hypothesis has been proposed to explain the decline in oestrogen protection with advancing age. This model suggests that younger women may have availed of an effective time window for exposure to oestrogen-containing HRT while older women may have missed this opportunity [34]. This was addressed in the Early versus Late Intervention Trial with Estradiol (ELITE) study which targeted women in early post-menopause and women in late post-menopause [43]. The goal was to determine whether time since menopause modified the effect of 17β estradiol on specified health outcomes, including cognitive change (ELITE-Cog). No significant relation was found for both post-menopause groups, between serum concentrations of free 17β estradiol and verbal episodic memory, executive functions or global cognition [43]. It was concluded that hormone associations may better reflect short-term activation effects on cognition mediated by changes in electrical properties and synaptic plasticity than possible long-term processes mediated by organizational changes within the brain.

4. Late-life cognitive outcomes of hysterectomy combined with hormone replacement therapy

Applying a retrospective method, the effects of hysterectomy have been analysed along with the age at surgery, anaesthesia method, and operation type on the late-life cognitive decline and risk of developing dementia [44]. In a large cohort of patients who underwent a hysterectomy, 1.7% developed dementia. Age at surgery and the anaesthesia method were positively associated with dementia occurrence, independent of operation type. Among patients 30–49 years of age, general anaesthesia (GA) was associated with a higher risk of late-life dementia than spinal anaesthesia (SA), with the risk of dementia increasing by 7.4% every year. In patients >50 years old, the risk of dementia increased by 13.0% every year. Therefore, it was inferred that the risk of dementia in women who underwent hysterectomy was significantly affected by age at surgery. The risk of dementia did not increase linearly with age but showed instead an S-curve with an exponential rise at about 50 years of age. The effect of the anaesthesia method (GA versus SA) was greater in the patients <50 years group. In contrast, the type of surgical procedure was not associated with the risk of dementia [44]. It was concluded that for women above 50 years of age at hysterectomy, surgery is an important factor influencing the odds of late-life dementia [44].

A report by Imtiaz and co-workers analysed whether oophorectomy, hysterectomy, and hysterectomy with bilateral oophorectomy could impose a risk of Alzheimer's dementia and whether the risk could be modified by hormone therapy [45]. The study included women with clinically verified AD, with results showing that all three surgeries were associated with a lower risk of AD among women without a history of uterine/ovarian/cervical cancer, although the absolute risk difference was small. The association was not evident in women with uterine/ovarian/cervical cancer history and was not modified by HRT use, which independently influenced the AD risk, with longer use showing a protective effect [45]. The study concluded that oophorectomy with or without hysterectomy after the start of natural menopause was not an important determinant of AD risk in older age. By combining results from the Mayo Clinic Cohort Study of Oophorectomy and Aging (MCSO) and a Danish Nationwide Cohort Study of women with hysterectomy alone, hysterectomy with unilateral oophorectomy, and hysterectomy and bilateral oophorectomy, Rocca and co-workers found that the extent of gynaecologic surgery correlated with a proportional increase in the odds of cognitive impairment or dementia [46]. Compared to women with no gynaecologic surgeries, the risk of cognitive impairment or dementia was increased in women who had hysterectomy alone, which was further increased in those with hysterectomy plus unilateral oophorectomy and increased even further in those with a hysterectomy and bilateral oophorectomy. The odds of dementia also increased with younger age at the time of surgery [46]. The authors concluded that oestrogen deficiency appeared to play a significant role in the development of late-life dementia, as women in the MCSO who underwent bilateral oophorectomy before the age of 49 years but were treated with oestrogen until at least age 50 years showed no increased risk of cognitive impairment or dementia [46].

Gilsanz and co-workers analysed the association between oestrogen exposure during the reproductive period of women with

hysterectomies, and the risk of dementia in a diverse population [47]. In a large cohort, Cox proportional hazard models evaluated the significance of the relationship between aspects of reproductive lifespan and dementia risk by adjusting for demographics and life course health indicators [47]. The study found that risks of dementia after adjustments for demographics and life course health indicators is higher in women that experienced menarche at ages equal to or above 16 years [47]. Natural menopause at ages under 47.4 was also associated with the elevated odds of dementia. Finally, reproductive lifespans that are under 34.4 years were associated with a 20% elevated dementia risk, with hysterectomies linked with 8% higher odds of late-life dementia [47]. It can be inferred from these studies that endogenous oestrogen has a protective influence against cognitive dysfunction. Removal of reproductive organs and the sources of oestrogen production during the reproductive age elicits a protracted vulnerability towards cognitive impairment in later life.

5. Late-life cognitive outcomes of *trans*-gender hormonal therapy

Hormone therapy is an integral part of gender transition and reassignment. Exogenous female hormones are used to help feminize *trans*-gender women, while anti-androgens are used as adjuncts to help suppress masculinizing features [48,49]. Different formulations, their advantages and drawbacks have been reviewed [50]. Van Heesewijk and co-workers reviewed the effects of long-term gender-affirming hormone therapy (GHT) on the cognitive function of *trans*-gender women in comparison to *cis*-gender men and women, testing the hypothesized improvements of cognitive performance in *trans*-gender individuals [51]. *Trans*-gender women who received GHT for at least ten years were compared to age and education-level matched cohort consisting of women and men. Cognitive functioning was assessed using Mini-Mental State Examination (MMSE), Category Fluency analysis, Letter Fluency D, and 15-Word (15WT) test for immediate and delayed recall [51]. *Trans*-gender women were more like men than women regarding cognitive performance. They differed significantly from women on MMSE and 15WT immediate and delayed recall. Scores were lower for *trans*-gender women on 15WT immediate and delayed recall, but they scored higher on MMSE. The cognitive differences between *trans*-gender women and *cis*-men or women were small but signifiant. The authors concluded that long-term GHT had minimal effects on the cognitive function of older *trans*-gender women [51].

Circumstantial evidence suggests that *trans*-gender adults experience a greater number of health disparities that are considered risk factors for dementia, e.g., higher cardiovascular disease, diabetes, tobacco/alcohol use, depression, and obesity [52]. They also experience social inequities linked to cognitive impairment, including a subjective cognitive decline (SCD), a self-reported experience of confusion or memory loss that is happening more often and getting worse in AD. Finally, *trans*-gender individuals are nearly twice as likely to report SCD and more than twice as likely to report SCD-related functional limitations, such as the reduced ability to work, volunteer or be social than *cis*-gender women or men [52]. The prevalence of depression was significantly higher for *trans*-gender and gender nonbinary adults as compared to *cis*-gender adults. Additionally, reports of cognitive disability, a surrogate for SCD, were higher in *trans*-gender and nonbinary adults compared to *cis*-gender adults [52]. Another study based on the data from the Behavioural Risk Factor Surveillance System (BRFSS, 2015–2019) survey found that about 17% of *trans*-gender adults reported SCD, which is higher than the 10.6% rate for *cis*-gender adults [53]. Among these individuals, the former were about three years younger and more likely to be a racial or ethnic minority and to have higher rates of depression. Using the same data, researchers found that *trans*-gender and gender non-binary (TNB) adults experience almost twice the higher rate of depression compared to *cis*-gender adults. Reports of cognitive disability were also significantly higher in TNB respondents compared to *cis*-gender respondents [53]. Assuming the exogenous hormonal impact in *trans*-gender women, an absence of a biological protective effect against cognitive impairment would have to be inferred.

6. Summary and conclusion

The life course dynamics of reproductive hormones and associated neuro-behavioral changes play an important role in shaping cognitive, emotional, and social behaviours. Baseline sex differences in cognitive performance and changes in the cognitive functioning in the course of aging have been widely reported, with reproductive senescence in women affecting mental health and brain mechanisms in late-life, as well as the risk of developing dementia. Although the bulk of the mechanistic and clinical evidence supports the ameliorative role of endogenous and exogenous gonadal hormones in cognition, there is a significant number of conflicting reports showing no association between reproductive senescence in women and cognitive decline, with a range of important questions remaining unanswered. The reasons for inconsistencies are at present unclear, with increasing evidence implying that the mid- and late-life cognitive outcomes of reproductive hormone use depend on multiple factors, including the timing and mode of intake, reproductive history, personal differences in biochemistry and genetics, with greater benefits reported in late-life typically associated with multiple factors. Despite major knowledge gaps, over recent decades, the use of gonadal hormones for reproductive control, replacement therapy for emotional and cognitive symptoms of menopause, gender transition and oophorectomy symptoms has been rising steeply. Emerging from this review is the acknowledgment that the field warrants in-depth mechanistic studies with well-controlled clinical trials to define the variables determining differential cognitive outcomes of the manipulations of gonadal hormones. Addressing the outstanding questions and elucidating mechanisms behind the late-life cognitive effects of gonadal hormone adjustments are expected to shed further light on the neurobiological underpinnings of sex-related cognitive differences. They also may explicate the mechanisms of cognitive decline and dementias in elderly with and without neurodegenerative diseases, thereby improving their diagnosis and treatment outcomes.

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Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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