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Progesterone and human cognition

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Abstract

Progesterone is a neurosteroid and a neuroactive steroid, produced primarily by the corpus luteum and the placenta. In some animal models, progesterone affects cognitive performance, and its potential role in human cognition is especially germane to women. This role can be investigated through associations between peripheral concentrations of progesterone in blood or saliva and neuropsychological test results, through differences in cognitive profiles between women using menopausal hormone therapy with and without a progestogen, and through clinical trials. In naturally cycling reproductive-age women and pregnant women, there is no consistent relation between progesterone levels and cognition. In postmenopausal women within 6 years of menopause and not using hormone therapy, progesterone levels are positively associated with verbal memory and global cognition, but reported associations in older postmenopausal women are null. Some observational studies of postmenopausal women using hormone therapy raise concern of a small deleterious cognitive effect of progestogen (medroxyprogesterone acetate was most often reported in these studies), but this association may due to confounding factors. Small, short-term clinical trials of progesterone show no meaningful effect on cognition. The quality of evidence is low, but overall findings do not reveal consistent, clinically important effects of progesterone on cognitive function in women.

Keywords

Cognition; menopausal hormone therapy; progesterone; menstrual cycle; postmenopause; pregnancy

Introduction

Progesterone is a 21-carbon sex steroid synthesized from cholesterol by way of pregnenolone. Progesterone is produced principally in the corpus luteum of the ovaries and by the placenta. It is also a neurosteroid (produced by nervous system tissues) and a neuroactive steroid (acts directly on nervous system tissues). Within the nervous system, progesterone is produced by neurons and glia. Enzymes required for the conversion of cholesterol to pregnenolone and the conversion of pregnenolone to progesterone are widely distributed within the brain. It can be metabolized to neuroactive metabolites, the most

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important of which is allopregnanolone. Progesterone is also secreted in small amounts by the adrenal glands, Leydig cells of the testes, adipose tissue, and other tissues.

Progesterone has multiple signaling pathways. It exerts its physiological effects primarily by binding to intranuclear progesterone receptors. The two main receptor isoforms, progesterone receptor-A and progesterone receptor-B, are found throughout the brain, and the expression and regulation differs for these two receptors¹. There is also a third isoform, and progesterone binds to several membrane receptors and has other mechanisms of action. Progesterone is antagonistic to some effects of estradiol in the brain, but the relation is complex and their actions are at times synergistic^{2,3}. Both play key roles in synaptic plasticity and neuroprotection². Neuroprotective effects of progesterone have been demonstrated in animal models of traumatic brain injury, spinal cord injury, stroke, and neurodegeneration. However, results of human trials of progesterone for neuroprotection after traumatic brain injury are disappointing^{4,5}. There is convincing evidence, at least in rodents, that progesterone enhances object memory and affects other cognitive abilities⁶. In cycling cynomolgus monkeys, however, the concentration of serum progesterone was associated with poorer performance on a discrimination task and was unrelated to other cognitive performance measures⁷.

Approaches to the study of progesterone and cognition

Progesterone circulates in both women and men. Questions of cognition are particularly relevant to women, because endogenous progesterone production is higher in women during early adulthood, when it is produced by the corpus luteum or placenta, and because menopausal hormone therapy often includes progesterone or another progestogen. Very few studies have considered the influences of progesterone on cognition in men.

There are several approaches to the study of cognitive effects of progesterone in women (Table 1). Progesterone is highly lipid soluble and readily diffuses across the blood–brain barrier. One approach is to examine the association of progesterone concentrations measured in blood or saliva in relation to cognitive performance. If progesterone has important effects on cognition, then peripheral levels should be associated with neuropsychological test results.

Menopausal hormone therapy provides the opportunity to examine the relation between progestogen and cognition by comparing cognitive performances of women using estrogen alone and women using estrogen plus a progestogen. Differences, if any, might be ascribed to the progestogen, if plausible alternative explanations can be excluded. Finally, the most convincing evidence for cognitive effects of progesterone would come from well-designed, adequately powered, randomized trials of progesterone compared to placebo.

Progesterone levels and cognitive associations

Progesterone concentrations can be measured by radioimmunoassay in blood and saliva, and these values can then be analyzed in relation to results of concurrent cognitive testing. These associations have been examined in women of reproductive age during different phases of

the menstrual cycle and during pregnancy, and they have been examined in older women after the menopause.

Associations in naturally cycling women

During a woman's reproductive years, blood and salivary concentrations of progesterone are low during the early follicular phase of the menstrual cycle, increase during the luteal phase as the corpus luteum develops and, if the ovum remains unfertilized, decline as the corpus luteum regresses prior to menses. Because estradiol levels also increase during the luteal phase of the cycle, it is difficult to tease out cognitive effects of progesterone from those of estradiol simply by examining cognitive changes over the course of the menstrual cycle.

A number of studies have examined cognitive performance on various tasks in naturally cycling women. Some investigators report differences based on menstrual cycle phase, although others do not. Such differences, when found, may implicate better performance on perceptual-spatial tasks (often viewed as male-advantaged) during the menses or early follicular phase, when estradiol and progesterone levels are low, and better performance on fine motor tasks (often viewed as female advantaged) during the luteal phase, when levels of both hormones are higher⁸. Cognitive findings, however, have been inconsistent, perhaps due to small sample sizes and methodological differences between studies or perhaps, instead, to the absence of any true effect. Moreover, most studies report no association between serum or salivary progesterone concentrations and cognitive performance⁹⁻¹⁶.

The largest of these studies involved 88 women aged 18-40 years in Germany and Switzerland¹³. These participants were assessed at four time points across one or two menstrual cycles with computerized tests of divided attention, visual working memory (block span forwards and backwards), and executive function (cognitive bias test). Blood levels of progesterone showed no consistent relation to cognitive performance.

Information can be processed holistically or piecemeal, and it is suggested that attention to global and local features may be influenced by progesterone. These differences in approach could affect navigational skills. A common global-local paradigm uses a single large figure (for example, the letter A) composed of smaller, different figures (for example, the letter U). There may be sex differences in how global-local information is processed, with men tending to use a more holistic strategy and women a more decomposed, detail-oriented strategy¹⁷. Twenty-two college students in the follicular phase and 19 in the luteal phase of the menstrual cycle were tested with global-local tasks¹⁸. In this study, women identified global targets more rapidly than local targets, but the global advantage was reduced for women in the luteal phase compared to women in the follicular phase. For one of the experimental paradigms, salivary progesterone was inversely related to the global advantage for women in the luteal phase.

There is suggestive evidence that progesterone might potentiate memory specifically for emotionally laden material. Intrusive memories, for example, are more common during the luteal phase of the menstrual cycle, and their frequency correlates with salivary progesterone levels¹⁹. This theory was assessed in 60 undergraduates, who viewed images that had either a negative valence or neutral valence²⁰. Based on salivary hormone levels, women in this

study were classified as being in the follicular or luteal phase of the menstrual cycle. Free recall was assessed the following week, and recall of negative images – but not recall of neutral images – was better for women who had encoded images during the luteal phase of the cycle, when compared to women who had encoded images during the follicular phase. In both groups combined, salivary progesterone correlated positively with recall of emotional images²⁰. In contrast, salivary progesterone concentration was not associated with later recall of aversive images or neutral images in 40 college students shown images in the late follicular phase or the mid-luteal phase of the menstrual cycle²¹. In still another study, 38 university students in the early follicular or the periovulatory stage of the menstrual cycle were shown pictures, whose imagery valence was classified as pleasant, unpleasant, or neutral²². One week later, periovulatory women had better memory for pleasant images, and women who had been in the early follicular phase had better memory for unpleasant images. Compared to the early follicular group, women in the periovulatory group were better at recalling positive images. However, salivary progesterone concentrations failed to correlate with recall of pleasant, unpleasant, or neutral pictures.

Associations during pregnancy

Levels of several hormones – including estradiol, progesterone, testosterone, and cortisol – increase substantially during pregnancy. For progesterone, compared to the postpartum period, the difference can be quite large, as much as one to two orders of magnitude. In two small cohorts of pregnant women, neuropsychological performance was examined during the last trimester of pregnancy and again during the postpartum period. In a study of 19 women (average age 33 years)²³ and in a study of 55 women (average age 31 years)²⁴, there were differences in some cognitive scores between test sessions, but levels of progesterone were unrelated to test performances prior to delivery or after delivery.

Associations in postmenopausal women

After menopause, serum concentrations of progesterone are quite low (< 0.5 ng/ml) compared to about 5–20 ng/ml during the follicular phase of the menstrual cycle. Even within this low, physiological range, the variation in progesterone concentration is associated with cognitive function. In a cross-sectional analysis of 271 postmenopausal women within 6 years of menopause (mean age 55 years), concentrations of progesterone were significantly and positively associated with composite neuropsychological measures of verbal memory and global cognition, but not executive functions²⁵. In the same study, progesterone levels were unrelated to cognition in 372 postmenopausal women 10 or more years after menopause (mean age 65 years)²⁵.

Serum progesterone was also examined in relation to cognition in two smaller studies of older postmenopausal women. These did not specifically exclude current users of hormone therapy. Among 101 women (mean age 80 years), higher progesterone levels were associated with poorer clock-drawing performance several years later²⁶. However, in a study of 39 women (mean age 79 years), progesterone was unrelated to cognitive performance²⁷.

Menopausal hormone therapy and cognitive associations

Menopausal hormone therapy, an estrogen with or without a progestogen, offers an opportunity to examine the relation between progestogen and cognition by comparing cognitive performances of women using estrogen alone and women using estrogen plus a progestogen. This comparison can be made in observational cohorts and in clinical trials of hormone therapy where progestogen use is tied to estrogen use but is not itself randomly allocated. In these settings, cognitive differences, if any, might be attributed to the presence or absence of the progestogen. This approach is only possible in cohorts where analyses are reported separately for these two groups of hormone users.

There are important caveats. Women who use unopposed estrogen (observational cohorts) or who are allocated to estrogen-alone (clinical trial cohorts) differ from women who use an estrogen plus progestogen or are allocated to combined therapy. Many postmenopausal women who take unopposed estrogen or who would have been allocated to unopposed estrogen have had a hysterectomy and do not require progestogen to protect the uterus from the risk of endometrial cancer. Some of these women had ovaries removed at the time of hysterectomy (surgical menopause). Compared to natural menopause, surgical menopause occurs abruptly and at an earlier age than it would have otherwise²⁸. Even when ovaries are conserved, hysterectomy before menopause is associated with an earlier age of natural menopause²⁹. There are other differences. Surgically menopausal women have lower androgen levels than naturally menopausal women³⁰, and androgens have the potential to affect cognition. There are important demographic differences between women with and without a uterus^{31,32} and, more generally, surgically menopausal women face higher risk of adverse health outcomes and excess mortality³³.

Observational cohorts of postmenopausal women

A cohort of Japanese–American women aged 65 years and older (mean age at baseline, 71 years) were tested on two occasions 2 years apart with the Cognitive Assessment Screening Instrument, a measure of global cognitive ability³⁴. A total of 132 current users of unopposed estrogens showed slight improvement on this 100-point instrument (2-year rate of 1.7 points). In contrast, 64 current users of estrogen and progestogen showed a small decline (−0.4 points). In this cohort, medroxyprogesterone acetate (MPA) was the only progestogen reported.

Investigators in the Nurses' Health Study examined the relation between menopausal hormone therapy and cognitive decline³⁵. The health profile was slightly better for nurses reporting current use of estrogen plus progestogen compared to women reporting only estrogen. When compared to women who had never used hormone therapy, current users of an estrogen plus progestogen were at somewhat greater risk of substantial cognitive decline than current users of estrogen only. For example, the relative risk (95% confidence interval) for large decline on the Telephone Interview for Cognitive Status was 1.27 (0.97–1.66) vs. 1.04 (0.85–1.28), and for a verbal memory composite score it was 1.41 (0.91–2.19) vs. 1.10 (0.76–1.57).

Clinical trial cohorts of postmenopausal women

Several large, long-duration trials have examined cognitive effects of hormone therapy in healthy postmenopausal women without dementia. Of these, only the Women's Health Initiative (WHI) trials and the Early versus Late Intervention Trial with Estradiol (ELITE) reported separate outcomes in subgroups identified by progestogen use. In these trials, active treatment consisted of estrogen alone (women without a uterus) or estrogen with a progestogen (women with a uterus). Any differences in the treatment effect – estrogen-alone minus placebo compared to estrogen-plus-progestogen minus placebo – might be attributed to the progestogen.

Women's Health Initiative trials—In the WHI Memory Study trials, cognitive effects of hormone therapy were assessed among women aged 65–79 years. Women without a uterus were randomly assigned to conjugated estrogens (0.625 mg) or placebo (estrogen-alone trial); women with a uterus were assigned to conjugated estrogens plus MPA (2.5 mg) as a continuous combined formulation or to placebo (estrogen-plus-MPA trial). Women were assessed with the Modified Mini-Mental State Examination, a test of global cognition, at baseline and yearly intervals. A subset of women were assessed later with a more extensive neuropsychological battery. Results were published separately for women with^{36,37} and without^{38,39} a uterus, and for global cognition^{36,38} and detailed neuropsychological test scores^{37,39}.

Analyses of global cognition involved 4381 women in the estrogen-plus-MPA trial and 2808 women in the estrogen-alone trial^{36,38}. After mean follow-ups of 4.2 and 5.4 years, respectively, there were small differences in global cognition, the magnitude of which was not clinically meaningful. Women in all groups tended to improve during the course of the trial (practice effect), with placebo groups improving slightly more than hormone therapy groups. For women with a uterus, the mean difference between the estrogen-plus-MPA group and the placebo group was –0.18 points on a 100-point scale³⁶. For women without a uterus, the mean difference between estrogen-alone and placebo was –0.26 points³⁸.

About two-thirds of eligible trial participants consented to detailed neuropsychological assessment, referred to as the WHI Study of Cognitive Aging^{37,39}. This started about 3 years after treatment began, when the average age of trial participants was 74 years, and testing was repeated annually for up to 3 years. Results were reported as rates of change in test scores. As with global cognition, average neuropsychology scores tended to improve in all treatment arms.

Estrogen-plus-MPA analyses involved 1416 women with a uterus. When women in the active treatment group were compared to the placebo group, the rate of change was slower (worse outcome) for verbal memory (assessed with the California Verbal Learning Test), faster (better outcome) for visual memory (assessed with the Benton Visual Retention Test), and not different for spatial ability or other cognitive domains³⁷. For 886 women without a uterus, unopposed estrogen compared to placebo was associated with reduced rate of change (worse outcome) on spatial ability (card rotation task), but other comparisons – including verbal and non-verbal memory – did not differ between treatment groups³⁹. There were no effects on mood in either study.

The between-trial differences (memory in the estrogen-plus-MPA trial; card rotation in the estrogen-alone trial) were not compared directly, and treatment effects were small. It is possible that MPA, when combined with conjugated estrogens, improves card rotation performance and visual memory and impairs verbal memory relative to conjugated estrogens alone. However, women in the two trials are distinguished by demographic differences³², and small treatment effects on only a subset of neuropsychological tasks suggest, alternatively, the absence of meaningful cognitive effect of MPA in this setting. For global cognition^{36,38}, inferences are similar; hormone–placebo differences were nearly identical for women with a uterus (exposed to MPA) and those without (not exposed to MPA).

Early versus Late Intervention Trial with Estradiol—ELITE was designed specifically to test the timing, or critical window, hypothesis of menopausal hormone therapy⁴⁰. As applied to cognition, the hypothesis states that initiation of hormone therapy by younger postmenopausal women near to the time of menopause improves cognition, whereas initiation by older postmenopausal women further from the time of menopause has no benefit and may be harmful. Active treatment in ELITE was with oral estradiol, 1 mg daily. Women with a uterus also received micronized progesterone as a 4% vaginal gel, one daily application for 10 days each month, or a placebo gel. For this trial, women were recruited in two postmenopausal groups: within 6 years of menopause ($n = 271$, mean age 56 years) and 10 or more years after menopause ($n = 372$, mean age 65 years)⁴¹. After 5 years, hormone therapy had no significant effect on a verbal memory composite score (primary outcome) or on composite scores for executive functions or global cognition; this was the case for both postmenopausal strata. Findings were similar in women with and without hysterectomy⁴¹, a result that indicates the absence of a progesterone effect. This conclusion is tempered by the fact that only 60 trial participants had undergone hysterectomy. Moreover, although vaginal delivery of micronized progesterone increased serum progesterone concentrations significantly, the systemic exposure of the topical preparation was less than would be expected with oral administration.

Direct evidence from clinical trials

Cognitive endpoints obtained during a clinical trial of a progestogen versus placebo provide the strongest evidence of whether a progestogen improves or impairs cognition. However, only a few studies have examined acute or short-term cognitive effects of progestogen directly, and sample sizes have been small. No study has considered long-term cognitive effects.

Clinical trials of cycling women

Acute effects of single doses of oral micronized progesterone were assessed within a crossover design in 24 women, aged 18 to 24 years⁴². Women were placed on an oral contraceptive for two weeks and then were given micronized progesterone (300 mg, 600 mg, or 1200 mg) or placebo. The order was randomized, and each dose was separated by at least a week. Cognitive testing immediately prior to drug ingestion assessed information processing speed (measured by the digit symbol substitution test) and word-list recall, and testing was repeated hourly for 4 hours and again at hour 6. Blood was obtained

concurrently for progesterone levels, and analyses used test scores at the time of the peak level. Women in this study reported fatigue in a dose dependent manner. Progesterone was associated with reduced immediate recall (but not delayed recall) on the list-learning task; the comparison with placebo was significant only for the 600 mg dose. The absence of a dose effect implies that this finding may have occurred by chance. Mood was unaffected. In post hoc analyses of the 12 women achieving the highest plasma levels of progesterone at the supraphysiologic 1200 mg dose, information processing speed and word list delayed recall were reduced compared to placebo⁴².

Eight women aged 18 to 35 years received a single intramuscular injection of progesterone (100 mg) or placebo (once each) during the early follicular phase of two menstrual cycles⁴³. Relative to placebo, progesterone led to a small improvement in information processing speed (digit symbol substitution test) but not verbal memory (word list recall).

Clinical trials of postmenopausal women

Short-term effects of progestogen have been assessed in small trials of postmenopausal women. Ten women aged 50–72 years received single intramuscular injections of progesterone (25 mg, 50 mg, 100 mg) or placebo in random order at weekly intervals⁴³. There were no effects of progesterone compared to placebo on concurrent tests of information processing speed or verbal memory.

Thirty-five women aged 58–75 years who had undergone hysterectomy were randomly allocated to oral estradiol (2 mg) and progesterone (100 mg), estradiol alone, or placebo in a parallel-groups trial⁴⁴. This design allows for comparisons between the estradiol-alone group and the estradiol-plus-progesterone group. Cognitive testing involved nine tests (paragraph recall, verbal paired associates, visual paired associates, digit and block spans, letter cancellation, the Stroop color–word interference test, verbal fluency, and mental rotation), and results at 4 and 24 weeks did not differ among treatment groups.

In a cross-over trial of 10 women aged 54–70 years, women were assigned to oral micronized progesterone (300 mg) or placebo for 21 days, separated by a 2-week wash-out period. Progesterone had no effect on tests of attention, aspects of executive functioning, or verbal memory⁴⁵.

Cognitive effects of progesterone and a progestin were directly compared with each other and with placebo in a 12-week, three-arm randomized clinical trial of 24 younger postmenopausal women (mean age 55 years; seven to nine women in each group)⁴⁶. All women received conjugated estrogens (0.625 mg) and, in addition, were assigned to cyclic oral MPA (10 mg), micronized progesterone (200 mg), or placebo. There were significant differences on two of the cognitive tasks used in this study. Verbal memory – assessed by delayed recall on a paired-associates learning task – was better for women in the MPA group compared to women in the micronized progesterone group or the placebo group. Working memory – assessed with a digit span backwards task – was better for women in the micronized progesterone group compared to women in the MPA group or in the placebo group⁴⁶. There were no between-groups differences in other cognitive performances (mental rotations, trail-making test, and recall of a paragraph story). The differences in verbal

memory and working memory were not specifically predicted a priori and are difficult to interpret.

Thirteen recently postmenopausal women (average age 51 years) were assessed in a cross-over study of progesterone (200 mg) or placebo, each taken for 12 weeks⁴⁷. Performances on six cognitive tasks were similar after both treatments, but progesterone compared to placebo was associated with changes in brain activation during functional magnetic resonance imaging.

Other approaches

A number of researchers have examined cognition in women using oral contraceptives. Studies often involved a fixed-dose combination of an estrogen and progestin, where any progestin effect would be difficult to separate from an estrogen effect. An interesting observational study of 155 college students using oral contraceptives showed that women whose oral contraceptive contained a more androgenic progestin performed better on a visuospatial task (mental rotations) than women using other oral contraceptives⁴⁸. Hormone levels were not measured. A smaller study of university students reported longer reaction times on a mental rotation task for women using more androgenic oral contraceptives, but salivary concentrations of progesterone were unrelated to cognitive outcomes⁴⁹. In general, the quality of evidence on the impact of oral contraceptives on cognition is poor, and research findings are inconclusive⁵⁰.

Women with premenstrual dysphoric disorder may be especially sensitive to progesterone withdrawal during the luteal phase, although there is no clear relation between progesterone levels and premenstrual symptoms. These symptoms include affective lability, irritability, depressed mood, or anxiety. Small studies of women with premenstrual dysphoric disorder or premenstrual syndrome, a related but less severe disorder, suggest no cognitive differences⁵¹ – or subtle deficits in working memory^{52,53} – compared to reproductive-age women without premenstrual symptoms. Progesterone levels, however, are not associated with cognitive test findings⁵⁴, although data are sparse.

Mifepristone acts as a competitive progesterone receptor antagonist. This drug is best known as a key ingredient of emergency contraceptives. Mifepristone is also an antiglucocorticoid and a weak antiandrogen, and its cognitive effects therefore cannot be ascribed to progesterone blockade alone. Because of the effects on the type II glucocorticoid receptor, mifepristone has been considered for several neuropsychiatric disorders, including depression, Alzheimer's disease, and post-traumatic stress disorder. This compound improved verbal memory but not other cognitive results in a 6-week cross-over study of male Gulf War veterans with chronic multi-symptom illness⁵⁵. Mifepristone is also classified as a selective progesterone receptor modulator, and cognitive effects of other drugs in this class are yet to be reported.

Concluding perspective

There is a firm biological rationale for the view that progesterone plays an important role in brain function^{1,2}, and there are discernible effects on cognition in animals⁶. Moreover,

progesterone exposures are linked to patterns of brain activation during cognitive processing in women⁵⁶. However, it remains to be shown that endogenous progesterone or exogenous progestogens exert clinically meaningful effects on short-term or long-term cognitive function in healthy women.

Definite answers are, admittedly, difficult to come by. Clinical trial data are scanty. Trials involve small numbers of participants, are of short duration, and yield inconsistent findings. Although most progesterone is produced by non-neural tissues, progesterone is also made by neurons and glia, and changes in peripheral concentrations may be buffered or compensated by factors that determine tissue-level exposures in the brain.

There are other formidable methodological barriers. In observational studies of reproductive-age women, it is difficult to separate cognitive effects of endogenous progesterone from those of estradiol, and the dynamic interaction between the two suggests that it may not be meaningful to try to do so. Some reproductive-age women experience cyclic changes in mood, well-being, mental energy, and other behavioral traits. These changes, which may well be modulated by progesterone or progesterone metabolites such as allopregnanolone, have the potential to influence cognitive performance, but the impact of these factors is likely to be subtle and difficult to capture with standard neuropsychological instruments.

Most studies of younger women failed to confirm a relation between progesterone levels and performance on a variety of neuropsychological tests, although there is inconsistent evidence that progesterone might play a role in global-local processing, in the encoding of emotional memory, or perhaps other cognitive processes. The inference is that peripheral concentrations of progesterone within the physiological range experienced by women during the normal menstrual cycle do not have meaningful, acute or short-term effects on most aspects of cognition. It is possible, however, that larger studies would discern modest effects within specific cognitive domains.

Higher, sustained levels of progesterone occur during pregnancy and are followed by a very rapid decline after childbirth and delivery of the placenta. Small studies, which fail to discern a relation between progesterone levels and cognitive skills in late pregnancy or the early postpartum period, argue against a major cognitive role for progesterone in this setting.

Studies of postmenopausal women provide evidence on sustained progesterone exposures – as opposed to acute, short-term, or dynamic exposures – in the low physiological range that characterizes this reproductive stage and also in the higher physiological range achieved by the progestogen component of menopausal hormone therapy. One large study of women not taking hormone therapy showed a positive relation between serum progesterone and both verbal memory and global cognition²⁵. This association was evident only for relatively younger women who were on average about 3.5 years from the final menstrual period. This finding needs to be replicated, and there is yet no evidence that progesterone levels are related to cognitive function in older postmenopausal women.

As reviewed above, there are hints that MPA might have a deleterious effect on cognition in older postmenopausal women. The observational data are far from convincing, and the magnitude of the mean effect – if indeed present – is small and unlikely to be noticed by

individual women. It is important to note that progestins have a range of physiological and clinical effects, which vary from compound to compound⁵⁷. MPA and progesterone differ in their pharmacological properties, biological actions, and effects on learning and memory in animals^{57,58}, and it is not known whether progesterone, MPA, or a different progestin would affect human cognition in exactly the same way.

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Table 1.Cognitive effects of progesterone in adult women: common investigative approaches and results^a.

<i>Reproductive stage</i>	<i>Approach</i>	<i>Time frame^b</i>	<i>Results</i>
Normally cycling women	Peripheral progesterone concentrations	Acute	Generally null; possible associations with global/local processing or emotional memory
	RCT: progesterone compared to placebo	Acute	Inconsistent associations for information processing speed; otherwise null
Pregnant women	Peripheral progesterone concentrations	Short-term	Null associations
Postmenopausal women	Peripheral progesterone concentrations	Long-term	Early postmenopause: positive association for verbal memory and global cognition; null association for executive functions
			Late postmenopause: null associations
	Observational cohorts: estrogen + progestogen MHT compared to estrogen-alone MHT	Long-term	Null associations; possible negative associations for medroxyprogesterone acetate
	RCT: progesterone compared to placebo	Short-term	Null associations
	RCT: estrogen + progestogen compared to estrogen-alone	Short-term	Null association

^a See text for details. The quality of reported evidence is generally weak. Other approaches are feasible;^b acute, hours to days; short-term, weeks to months; long-term, years.

MHT, menopausal hormone therapy; RCT, randomized clinical trial.