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Review article

# A systematic review of the impact of oral contraceptives on cognition☆

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**Abstract**

Combined oral contraceptives (OCs) are the most commonly prescribed medication in women of reproductive age, but despite widespread use, their effect on cognitive performance remains controversial. Given strong evidence for the neurological impact of reproductive hormones, a clear rationale for investigation exists. This systematic review sought to identify, collate and critically appraise studies assessing the impact of OCs on cognition in healthy premenopausal women. Ovid MEDLINE, PsychINFO and EMBASE were comprehensively searched using relevant keywords for original peer-reviewed observational studies or randomised trials published after 1960. Of 1289 references screened, 22 studies were eligible for inclusion. Assembled evidence supports a cognitive impact of OCs restricted to specific domains; however, the quality of evidence is poor. The most consistent finding is improved verbal memory with OC use. Evidence is also emerging that differing progestin androgenicity may lead diverse OC formulations to differentially impact certain cognitive domains, such as visuospatial ability. At present, evidence is inconclusive, contradictory and limited by methodological inconsistencies. There is scope for further research in this area to definitively determine the cognitive impact of OCs.


*Keywords:* Oral contraceptives; Cognition; Estrogen; Progesterone; Progestins; Reproductive hormones

## 1. Introduction

Oral contraceptives (OCs) are the most commonly prescribed medication in women of reproductive age [1,2]. OCs contain synthetic analogues of estrogen and progesterone, which prevent pregnancy by centrally disrupting the hypothalamic-pituitary-ovarian axis and acting locally on reproductive organs.

The most commonly used estrogen analogue is ethinylestradiol [3], though recent innovation has seen the introduction of physiological forms of estrogen such as estradiol and estradiol valerate [4,5]. The progestin component is more diverse, with differing androgen receptor activity between agents. Some progestins such as levonorgestrel and norethisterone have higher androgenicity, whilst some such as cyproterone acetate have minimal androgenic action whereas others like drospirenone are anti-androgenic [6–8]. Whilst the physical side effects of OCs are well established [9], the impact of OCs in the central nervous system, particularly on cognitive abilities, remains controversial.

There is, however, robust evidence that sex hormones can affect performance in specific cognitive tasks [10,11]. Sex hormone influence is thought to underlie cognitive differences between the sexes, i.e. that women generally perform better on verbal, fine motor and some memory tasks, whilst men perform better on visuospatial tasks [12]. In women, cognitive performance in female-favouring tasks is improved during the luteal phase, when estrogen levels are high (following their pre-ovulatory peak) and progesterone rises; whilst performance in male-favouring tasks is maximal during the menstrual phase [13,14]. Studies have correlated higher serum testosterone levels in women with polycystic ovarian syndrome with better performance in male-favouring cognitive tasks [15].

Based on the current literature, estrogen is generally understood to have a positive effect on cognitive performance (particularly in female-favouring tasks, such as verbal memory) [12,16,17] whereas progesterone has been observed to exert negative effects [11]. Paradoxically, both hormones exert neuroprotective actions in vitro [18–21] and are likely to interact in ways that are yet to be understood. Evidence is emerging that different synthetic hormone

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analogues may exert distinct cognitive effects [17,22]. The steroids found in OCs may also have indirect effects, for example, though suppression of other endogenous hormones including cortisol and testosterone [23].

The aim of this review was to collate and critically appraise the current literature examining the impact of OCs on cognition in healthy premenopausal women.

## 2. Methods

This systematic review was performed in accordance with PRISMA guidelines [24]. Observational studies and randomised trials evaluating cognitive impacts of OCs published in English after 1960 were considered. Studies were included if they involved (a) a study group of healthy premenopausal females taking OC medications at the time of evaluation and (b) at least one clinical measure of cognitive performance assessing one or more of the following domains: attention, memory, executive function (EF), verbal and visuospatial abilities, social cognition and emotional processing, and if they (c) included either a separate control group of naturally cycling women or had OC users act as their own controls by performing repeated cognitive evaluation in the active versus placebo pill phases, or both. Exclusion criteria were (a) retrospective studies based on reported historical OC use, (b) studies involving women with a medical illness and (c) studies involving administration of additional medications or study conditions with potential for cognitive impact, unless meaningful analysis of baseline evaluations was reported.

Ovid MEDLINE, PsychINFO and EMBASE were searched using combinations of the following terms: 'contraceptive', 'oral contraceptive pill', 'hormonal contraception' and 'birth control' and 'cognition', 'memory', 'cognitive function', 'verbal', 'visuospatial', 'attention', 'concentration', 'executive function', 'social' and 'emotional'. The most recent search was conducted on 7th January 2014.

References were collated in EndNote (Thomson Reuters, New York), allowing automatic and manual detection and deletion of duplicate articles. Title and abstract screening was performed independently by two reviewers (A.W. and R.W.) with arbitration by a third (clinical neuropsychologist (C.G.) where necessary. The reference lists of included texts were screened for additional relevant papers. Multiple papers arising from the same author group were crosschecked to ensure there was no duplication of data. Where this occurred, only one paper was included.

Information retrieved from eligible studies included study design, number of participants, characteristics of study population(s), types of OCs taken by participants, cognitive assessments performed and significant findings. The cognitive tasks from each study were reviewed and evaluated by C.G. to determine which cognitive domains they assessed. Study quality was independently evaluated using the Cochrane Collaboration's Risk of Bias Assessment Tool for Cohort Studies [25] by two reviewers (A.W. and R.W.) with a third (C.G.) to arbitrate in the case of disagreement. Studies were rated as high, unclear or low risk of bias according to criteria described by the Cochrane collaboration [26].

## 3. Results

A total of 1289 potentially relevant articles were identified, of which 22 met the inclusion criteria detailed above. Characteristics and findings of eligible studies are summarised in Table 1.

### 3.1. Verbal memory

One of the more reliable findings in this area is an improvement in verbal memory with OC use [27,28]. In the Gogos study, this advantage was seen in OC users compared to non-OC users (though assessment was unblinded), whereas in the Mordecai study, improvement in verbal memory was seen in the active OC pill phase compared to the placebo pill phase. Improved verbal memory in OC users has not been uniformly observed however, with work by Islam [29], Wharton [30] and Gordon and Lee [31], finding no difference with OC use. However Gordon and Lee's study was rated high risk of bias due to inadequately matched groups and a lack of blinding. No studies to date have demonstrated a negative impact of OCs on verbal memory.

### 3.2. Visuospatial cognition

Visuospatial ability, a traditionally male-favouring domain, has been the area of greatest research interest. The majority of studies in this field (including those with the lowest risk of bias) have found no significant difference between OC users and non-users [27,28,31,29,32]. However, some have shown improvement in visuospatial ability [33–35] and one has shown impairment [36], using a variety of tasks and a broad range of OC formulations. Wharton et al in 2008 [30] was the first to analyse performance by OC subtype. They too found no *overall* difference in visuospatial ability between OC users and non-users, however when performances were grouped according to the androgenicity of the OC formulation, it was found that users of OCs containing testosterone-derived androgenic progestins (e.g. levonorgestrel) showed *enhanced* visuospatial ability, whereas users of new-generation pills with anti-androgenic progestins (e.g. drospirenone) had *impaired* visuospatial performance. Though the authors failed to blind assessments, their methodology was otherwise sound. Wharton proposed that differing androgenicity may provide an explanation for inconsistencies in previous literature regarding the visuospatial impact of OCs, with the opposing effects of anti- and pro-androgenic progestins potentially masking one another, such that there may falsely appear to be no overall impact of OCs in this domain.