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REVIEW ARTICLE

Relationship between sex hormones, reproductive stages and ADHD: a systematic review

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Abstract

Objective This systematic review aims to summarize current available evidence for the relationship between sex hormones or reproductive life stages (adrenarche in males and females, menarche, pregnancy, postpartum and menopause) and ADHD.

Methods We systematically reviewed studies investigating the relationship between sex hormones and symptoms of inattention and/or hyperactivity in individuals with an ADHD diagnosis or equivalent assessment of symptoms with validated scales. Articles were screened sequentially by two reviewers who were clinically and academically familiar with ADHD. Studies were rated according to Oxford Levels of Evidence (CEBM 2009).

Results Four studies matched inclusion criteria. One article was a case report of a female with ADHD and premenstrual syndrome experiencing worsening symptoms prior to each period (Quinn, J Clin Psychol 61:579–587, 2005). Another was a review article analysing literature relating to the effect of hormones on ADHD symptoms and supporting that a relationship exists between ADHD symptoms and sex hormone levels, without further characterization (Haimov-Kochman and Berger, Front Hum Neurosci 8, 2014). Giotakos and colleagues found no relationship between Wender Utah scores and sex hormone levels (Giotakos et al., J Forensic Psychiatry Psychol 16:423–433, 2005). An exploratory study by Ostojic and Miller found evidence for an association between early pubertal onset, inattention and risk-taking behaviour (Ostojic and Miller, J Atten Disord 20:782–791, 2016).

Conclusion The literature on the relationship between sex hormones and ADHD is limited. Available studies present contradicting information. It is not known how this lack of evidence affects the treatment of ADHD during the lifespan. Further research is required to correctly characterize the mechanisms behind ADHD symptoms and its potential association with sex hormones.

Keywords Sex hormones · Puberty · Inattention · Hyperactivity · ADHD

Introduction

Attention deficit and hyperactivity disorder (ADHD) is one of the most commonly diagnosed behavioural disorders in children, with an estimated worldwide prevalence of 5.29% (Polanczyk et al. 2007). ADHD is known to be more common in boys than in girls, with an approximate diagnosis rate of 4.2% in boys and 1.8% in girls (Cuffe et al. 2005). Approximately 2/3 of children diagnosed with ADHD will still have symptoms in adulthood (Zalsman and Shilton 2016). Sex differences also persist to adulthood. Adult women are more frequently diagnosed with inattentive subtype and less often diagnosed with the combined subtype compared to men (Biederman et al. 2004; Ramtekkar et al. 2010; Williamson and Johnston 2015). However, men report more severe attentional symptoms,

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while women report less impulsivity (Williamson and Johnston 2015).

Animal studies show a correlation between ADHD symptomology and endocrine and immune systems (Kozłowska et al. 2019). Using spontaneously hypertensive rats (a common animal model for ADHD), Kozłowska and colleagues showed that juvenile animals had elevated inflammatory markers such as interleukin-1 β and that adult rats, but not juveniles, had increased levels of adrenal steroids. They proposed that the increase in adrenal steroids may be a compensatory mechanism to modulate inflammation. Systemic inflammation has been associated with ADHD in children (Ardalan et al. 2019).

Several studies suggest hormonal states can affect cognitive abilities in healthy individuals (Matyi et al. 2019). For example, studies in menopausal women taking hormone replacement therapy have shown increased activation in the prefrontal cortex using fMRI but no clinical effects in cognition when assessed with neuropsychological tests (Frizell and Dumas 2018). A relationship between hormone levels and ADHD has been found in genetic hypogonadisms. A recent study found a three-fold increase in ADHD incidence in these patients, the risk being also associated with delayed puberty in this subgroup of children (Gotby et al. 2019).

Impulsive and addictive behaviour has been hypothesized to be influenced by the activation effects of sex hormones. Oestrogen presence has been shown to cause an increase in brain dopamine and serotonin concentrations and transporter availability in females, possibly leading to an increase in impulsivity. Testosterone has been linked to more impulsive decisions in males (Fattore et al. 2014; Goudriaan et al. 2010; Stanton et al. 2011).

Since life's reproductive stages are characterized by sex hormone fluctuations (see Table 1), it is possible that such changes affect ADHD symptoms. Males and females experience varied levels of hormone fluctuations throughout their development, which could also account for previously mentioned differences in symptom prevalence. Testosterone elevations in males could account for higher reported levels of hyperactivity when compared to females (Williamson and Johnston 2015). Additionally, children and adults experience differences marked by the onset and settling of puberty (see Table 1). Sex-based clinical differences in the presentation of ADHD are well known, but the physiological underpinnings of these differences have not been characterized in

Table 1 Summary of hormone level changes during life's reproductive changes. Modified from Best & Taylor's Physiological Basis of Medical Practice – 13th edition (Tandon and Tripathi 2012)

Sexual Life Stage	*Males*	*Females*
Puberty and fertile period	*Production of* ***gonadotropin-releasing hormone*** *causes:* - *Luteinizing hormone* ↑ - *Follicle stimulating hormone* ↑ - *Testosterone* ↑	*Production* ***of gonadotropin-releasing hormone*** *causes:* - *Luteinizing hormone* ↑ - *Follicle stimulating hormone* ↑ - *Estrogen* ↑
Pregnancy		*Estrogen* ↑ *Progesterone* ↑
Post-partum		*Estrogen* ↓ *Progesterone* ↓
Menopause		*Estrogen* ↓ *Progesterone* ↓
Andropause	*Testosterone* ↓	

detail (Haimov-Kochman and Berger 2014). A fluctuation in sex hormones as seen in physiological life stages—such as puberty, pregnancy and menopause—could lead to symptomatic changes in patients with ADHD which could alter the severity and type of symptoms expressed and therefore affect treatment and prognosis. The present study provides a systematic review of the literature to date on the relationship between sex hormones and ADHD.

Aim

A systematic review was conducted to identify the available evidence about the relationship between sex hormones on symptoms of ADHD, with an emphasis on the reproductive life stages, including adrenarche in males and females and menarche, menopause, pregnancy, and postpartum in females.

Methods

We performed a systematic review of studies investigating the relationship between sex hormones and ADHD during life's reproductive stages. The following electronic databases were searched: PubMed, CINAHL, PsycINFO, HealthStar, Embase, and Web of Science using relevant keywords (ADHD, sex hormones, pregnancy, estrogen, oestrogen, post-partum, progesterone, menopause, menarche, hormone replacement therapy, hormone blockers, transsexual health). We examined literature published in the last 30 years (Jan 1989 to September 2019). A grey literature search was also conducted, which included PhD repositories in Canada and internationally.

Studies were included if they investigated at least one group of patients with a clinical diagnosis of ADHD or equivalent assessment (validated scale or clinical interview for ADHD) and examined the association between sexual hormones or reproductive life stage on symptoms of ADHD.

We excluded conditions causing hypogonadism and hypergonadism, articles looking at exposure to maternal sex hormones while in utero, and articles looking at pathologies that affect sex hormones but are not part or the normal reproductive life stages (such as PCOS) (for titles, see Martel et al. 2009; Ohlsson Gotby et al. 2019). Articles were required to have abstracts in English irrespective of the language of the main text (articles with main text in English, German, French, Italian, Spanish, Portuguese, and Chinese were included in the search). Bibliographies of selected articles were scrutinized for additional resources that might have been missed in the primary database search. Articles selected were screened sequentially. Two authors independently reviewed all screened articles in order to build the final selection. The third author was consulted in case of disagreement. Reviewers were clinically and academically familiar with ADHD. The review's protocol followed Prospero guidelines (Moher et al. 2009). Studies were rated according to Oxford Levels of Evidence (CEBM 2016).

Results

We systematically searched six medical databases and screened 1499 manuscripts of which 40 were eligible for full text review; of these four titles matched the inclusion criteria (see Tables 2 and 3), two observational cross-sectional studies ($n=44$ and $n=253$, respectively), one narrative review, and a case study ($n=1$) (see Table 2). The screening process is detailed in Fig. 1. No randomized controlled trials were found. The studies were heterogeneous in nature and did not allow for any type of pooling. One of the four studies was limited to males, and one review focused on both sexes. The remaining two studies looked at females only (see Tables 2 and 3). We did not find any articles looking specifically at the effect of hormonal fluctuations due to pregnancy, menopause, or at the effects of hormonal treatments such as hormone replacement treatment in patients with ADHD.

We found limited evidence of hormonal influence in the symptomology profile of adults and children. Giotakos and colleagues administered the Wender Utah Rating Scale to 44 male adults (mean age 30.7) convicted of sexual assault. They analysed plasma hormone levels and found no relationship between Wender Utah scores and levels of testosterone, luteinizing hormone, follicle-stimulating hormone, free androgen index, or dihydrotestosterone (Giotakos et al. 2005). An exploratory study by Ostojic and Miller showed evidence of an association between early pubertal onset (measured using a modified version of the Pubertal Development Scale) in adult women and difficulty with attention (odds ratio = 1.270, $p=0.019$), emotion regulation (odds ratio = 1.070, $p=0.038$), and risky behaviour (odds ratio = 1.035, $p=0.045$) (Ostojic and Miller 2016). One non-systematic review article surveyed existing literature relating to the effect of hormones on ADHD symptoms. The authors hypothesized that both male and female sex hormones may influence neuronal circuits affecting emotional and cognitive responses, concluding that more research is needed (Haimov-Kochman and Berger 2014). Finally, Quinn reports a single clinical case in which addressing a female patient's ADHD and severe PMS symptoms was found to be essential in developing an appropriate treatment plan (Quinn 2005). The patient experienced worsening symptoms of both ADHD and PMS immediately preceding her period, and a clearer profile of her PMS symptoms was possible following treatment for ADHD (Quinn 2005).

Table 2 Summary of articles found investigating the relationship between sex hormone levels and ADHD symptomology. LOE*

Author/year	Type of study	N Male	N Female	Method of ADHD diagnosis	Results	LOE*
Giotakos et al. 2005	Observational (cross-sectional)	44 adults	0 adults	Wender Utah Rating Scale (WURS)	Findings suggest no association between history of ADHD and overall adult plasma sex hormone levels, as no significant difference was found between the two test groups (WURS ≤ 45 and WURS ≥ 46), testosterone ($F=0.67$, $p=0.42$), luteinizing hormone ($F=1.03$, $p=0.33$), follicle-stimulating hormone ($F=0.06$, $p=0.80$), free androgen index ($F=0.99$, $p=0.33$), and dihydrotestosterone ($F=0.28$, $p=0.60$)	2b
Ostojic and Miller 2016	Retrospective study	0 adults	253 adults	Barkley Adult ADHD Rating Scale–IV (BAARS-IV), Barkley Deficits in Executive Functioning Scale (BDEFS), Difficulties in Emotion Regulation Scale (DERS), The Risk-Taking Behaviour Questionnaire (RTBQ)	Early puberty was associated with ADHD symptoms; difficulty in attention (odds ratio = 1.270, $p=0.019$), emotion regulation (odds ratio = 1.070, $p=0.038$), and risky behaviour (odds ratio = 1.035, $p=0.045$)	2b
Quinn 2005	Case report	0 adult	1 adult	Clinical diagnosis. No scales used	Evaluation of the subject's premenstrual syndrome (PMS) symptoms allowed for a more accurate analysis of her behavioural and cognitive symptoms, leading to a more accurate diagnosis and improved treatment	5

*Levels of evidence

Table 3 Summary of review article found containing evidence of a relationship between sex hormone levels and ADHD symptomology. LOE*

Author/year	Type of study	Conclusion	LOE*
Haimov-Kochman and Berger 2014	Narrative review and opinion	The authors review the evidence for sex hormone influence on neuronal circuits and its effects on emotional and cognitive responses. They suggest that further studies looking at the interaction between menstrual cycle and ADHD may explain previous conflicting evidence in ADHD studies in women	5

*Levels of evidence

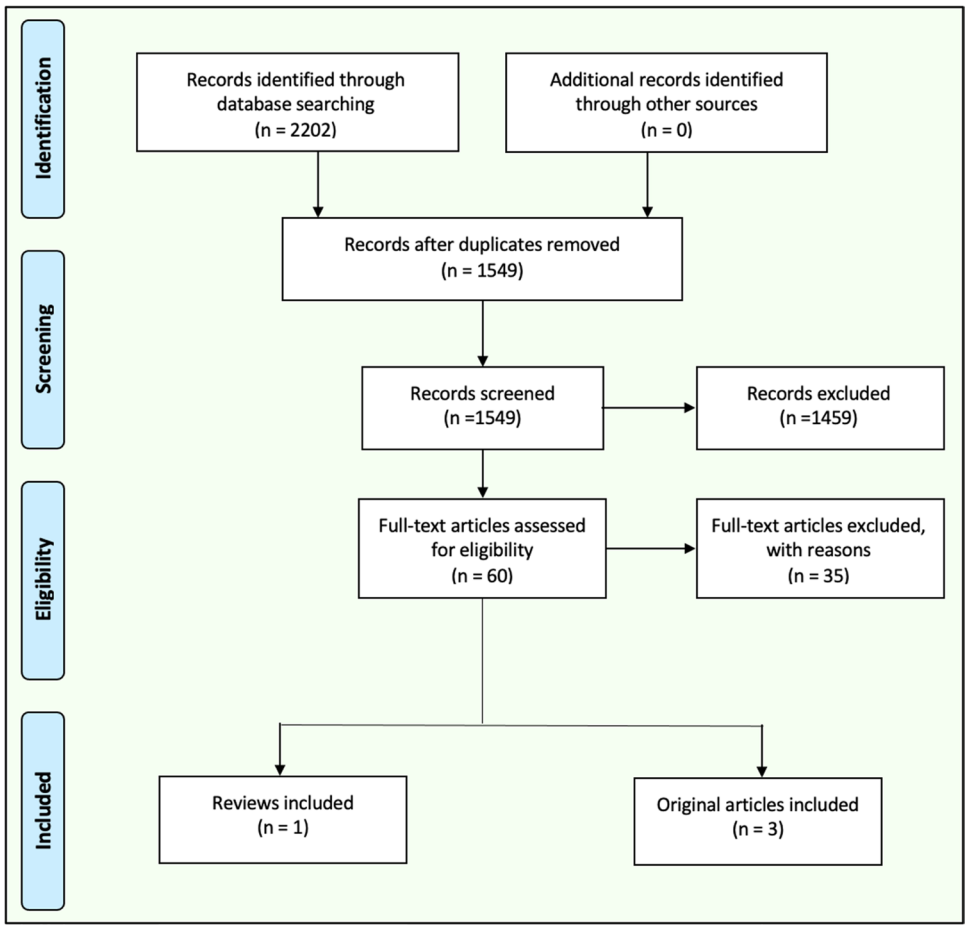

Fig. 1 Prisma diagram

Discussion

Despite a broad and comprehensive search, only four articles (three original studies and one narrative review) were found relating to the potential relationship between hormonal life stages and ADHD symptoms. ADHD is a common illness, but few studies have looked at the association of hormonal stages and ADHD symptoms in humans. We did not find any studies looking at this relationship specifically during pregnancy or menopause. Findings were heterogeneous and could not be compared or pooled. No RCTs were found. Small sample sizes and varying methodologies make the results difficult to generalize to the population at large.

The studies found regarding female ADHD symptoms and hormonal life stages highlighted the inconsistent and non-specific nature of available evidence. School-age girls with ADHD suffer more severe impairment than their peers without the disorder (Haimov-Kochman and Berger 2014); these girls were found to be more likely to suffer from comorbid disorders like anxiety and showed more difficulty in social interactions and relationships (Biederman et al. 1999). Interestingly, Ostojic and colleagues found that a child history of early pubertal onset was associated with ADHD symptoms in a sample of adult women (Ostojic and

Miller 2016). Gonadal puberty (gonadarche) is initiated by pulses of gonadotropin-releasing hormone (GnRH), while adrenal puberty (adrenarche) follows a separate pathway (Strauss et al. 2019). A complex cascade of physiological signals governs these processes, ultimately leading to an increase in circulating sex hormones. Given the limited available studies on the effects of puberty in ADHD, it is not possible to pinpoint the specific patho-physiological process implicated in early pubertal onset in children with ADHD. Gonadal hormones such as testosterone or oestrogen may play a role, but adrenal steroids such as dehydroepiandrosterone and androstenedione could also be key factors.

Notably, we did not find any studies investigating ADHD symptoms in other female physiological states such as pregnancy or menopause or looking at the response of patients with ADHD to hormonal treatments such as hormone replacement therapy. It is hypothesized that in women, hormonal cyclic fluctuations may affect ADHD symptoms (Roberts et al. 2018); however, we did not find any specific studies looking at the interaction of the menstrual cycle in women with ADHD. There are, however, varying levels of evidence indicating that variations in hormone levels lead to changes in attentional symptoms in healthy subjects and that some of these symptoms can be treated with stimulant medications (Shanmugan et al. 2016). Shanmugan and colleagues were able to show effective reduction in executive function impairment caused by menopause onset with Lisdexamfetamine treatment. However, given the small sample ($n = 14$), further research is required to confirm these findings (Shanmugan et al. 2016).

It is also possible that hormone fluctuations affect ADHD by increasing comorbidity. Additionally, comorbidity could result in an increase in symptom severity. Many psychiatric disorders appear for the first time during puberty. Early menarche has been linked to higher risk of depression and antisocial behaviour in adulthood. Depressive symptoms have been found to increase by a quarter in girls reaching menarche earlier than the average (Mendle et al. 2018). The one case report (Quinn 2005) highlighted the importance of assessing hormonal status in women with ADHD as part of a therapeutic plan. Comorbidity with other physical and psychiatric disorders is common in ADHD (Bolea-Alamañac et al. 2014); hormonal syndromes such as premenstrual dysphoric disorder may be more severe in women with ADHD and may require differential treatment but there is a paucity of studies on this comorbidity.

There is also evidence pointing at increased prevalence of depression in women with ADHD compared to men with ADHD, while men with ADHD are more likely to have a substance use disorder than women with ADHD (Williamson and Johnston 2015), these differential effects could be mediated by sex hormones. On the other hand, some studies found little difference in symptoms and impairment caused by ADHD between prepuberal boys and girls. In a study of Taiwanese children (age 11) with ADHD, boys and girls showed very similar results in cognitive tests and reported similar treatment needs (Yang et al. 2004), although it is important to note that symptomology in adults and in children is not necessarily comparable and is subject to fluctuations due to neurodevelopmental changes. For example, Giotakos and colleagues found no association between hormonal levels in male adults and ADHD symptoms (Giotakos et al. 2005). This may be related to the peculiarities of the sample used by Giotakos and colleagues: convicted adult males who may not be representative of the adult male population. It is also possible that an association exists in childhood that disappears in adulthood.

One significant limitation of this review is that most studies used validated scales but not necessarily a full clinical diagnosis. The majority of studies included offered a comparison based on reported symptoms of attention and hyperactivity disorder. However, in order to obtain a clinical ADHD diagnosis, adults must show symptoms as well as a level of functional impairment (American Psychiatric Association 2013). Therefore, studies reporting on symptoms recorded in a validated scale may not be enough for a clinical diagnosis if they do not examine the level of functional impairment across individuals.

The studies found did not address other sources of heterogeneity present in the population that may influence the effect of sex hormones. For example, individual variations in the number of dopamine receptors in regions like the hippocampal dentate gyrus and subventricular zone most likely influences symptomatic response, since it would make one more sensitive to hormonal fluctuations (Nussbaum 2012). Should that be the case, those experiencing hormonal fluctuations would present individualized physiological and behavioural responses that could manifest as ADHD or as other neurodevelopmental disorders. These individual differences cannot be characterized given the paucity of existing data. The lack of studies on the interaction between sex hormones and ADHD has led to a lack of understanding of the underpinning mechanisms behind the relationship between the reproductive life stages and the clinical presentation of ADHD.

Conclusion

Overall, the literature has not demonstrated a clear relationship between hormonal changes during life's reproductive stages and ADHD. The studies found, though limited in scope and quality, do point to some intriguing associations. Considering life's reproductive stages may help to develop more accurate diagnosis and more effective treatment options for ADHD patients. This systematic

review highlights areas in need of more research such as menarche and perimenopausal period to further characterize the relationship between sex hormones and ADHD symptomatology.

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Declarations

Conflict of interest The authors declare no competing interests.

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