

Should we consider sex hormone fluctuations relevant in the treatment of women with ADHD?

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Dear Editor,

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by notable gender differences in symptom presentation and medication response. Throughout the lifespan, women undergo multiple critical developmental phases associated with reproductive life events, including onset of menses, pregnancy, postpartum period and menopause, which are characterized by significant alterations in estrogen and progesterone levels. Moreover, from the onset of menarche to menopause, women experience cyclical monthly fluctuations in the levels of aforementioned ovarian steroid hormones (Bürger et al., 2024).

Some research suggests that hormonal fluctuations influence ADHD symptoms in women, raising the possibility that treatment response may vary across the menstrual cycle (Roberts et al., 2017; de Jong et al., 2023; Bürger et al., 2024). EEG patterns in depressive reactions connected to women's reproductive cycle have shown a correlation between a partial decrease in estrogen levels and the imbalance in the functioning of the brain's regulatory systems (Koshchavtcev, 2019). One of the mechanisms behind that, especially in ADHD, may be associated with the influence of estradiol (E2) (the major estrogen in females) on dopamine (DA) levels (Jacobs & D'Esposito, 2011; Roberts et al., 2017; de Jong et al., 2023). Impaired dopaminergic transmission is considered to play a crucial role in the etiology of ADHD and remains one of the main targets of pharmacological strategies in this disorder (Faraone, 2018). In women with low baseline DA levels, the late follicular phase, when E2 levels are high, was associated with neural patterns consistent with greater effective dopaminergic signaling in the PFC compared to menses, when E2 levels are low. In these women, high E2 levels were linked to improved performance specifically on high-interference working memory trials, whereas low E2 levels were associated with poorer performance (Jacobs & D'Esposito, 2011). However, women reported increased severity of ADHD symptoms not only at the time of menses, but also in the mid-luteal phase (Bürger et al., 2024; de Jong et al., 2023). During the follicular phase, when E2 was reaching its first peak, healthy women were more susceptible to stimulant drugs (White et al., 2002; de Jong et al., 2023). Nevertheless, only during the follicular phase, the increased response to stimulants was associated with high E2 levels (this relationship was influenced by a single high-value

observation) (White et al., 2002). On the other hand, during the luteal phase, the effects of stimulants were less intense, despite the secondary peak of E2, which was reported both in studies with healthy (White et al., 2002) and ADHD women (de Jong et al., 2023). Decreased levels of E2 in the context of increased levels of progesterone was associated with more pronounced ADHD symptoms in women with high trait impulsivity (Roberts et al., 2017; de Jong et al., 2023). These results suggest that E2 may enhance the response to stimulants in women, whereas high progesterone levels during the luteal phase can attenuate these drug effects (White et al., 2002; de Jong et al., 2023). This aligns with reports indicating that progesterone has demonstrated an attenuating effect on the euphoric response induced by psychostimulants (Jakovac et al., 2019). Furthermore, it was reported that healthy men exhibited similar responses to stimulants as healthy women tested during the follicular phase. However, the drug's effect in women tested during the luteal phase was significantly diminished compared to men, possibly due to high progesterone levels in females (White et al., 2002). Administering increased stimulant doses during the premenstrual phase indicated a positive trend in managing the worsening ADHD symptoms (de Jong et al., 2023). These data strengthen the argument that women with ADHD may require higher doses of stimulant medications based on hormonal levels and indirectly prove the risk of under- or over-dosing stimulant drugs, depending on the phase of the menstrual cycle at the time of dose adjustment.

A 2020 study by Lu et al. found that combining positive psychological information support with yoga exercises effectively alleviates depression and anxiety in menopausal women, improves sleep quality, and reduces overall menopausal symptom distress (Lu et al., 2020). During menopause, declining estrogen levels may also exacerbate ADHD-related symptoms. Emerging evidence suggests that these hormonal changes can influence both symptom presentation and treatment response (de Jong et al., 2023). Given these observations, the strategies proposed by Lu et al. (2020) may hold promise as an adjunct to stimulant medication for women with ADHD who experience symptom worsening during menopause, as well as during other hormonally sensitive periods such as the postpartum phase, the luteal phase, and the early follicular phase. Nevertheless, further research is needed to evaluate the effectiveness and clinical relevance of this approach.

Fluctuations in ovarian hormone levels throughout the menstrual cycle and their decrease during menopause and postpartum may be crucial when determining the appropriate dose of stimulant medication in women with ADHD. Since there is a notable deficiency in this area of research, in order to gather robust evidence, further well-designed studies involving large populations and considering different menstrual phases and hormonal life stages are necessary. Furthermore, it might also be valuable to explore the potential benefits of non-pharmacological strategies as adjunctive treatments. Acknowledging the gender specific approach to ADHD would signify the onset of a new paradigm in mental healthcare, providing more personalized therapeutic support.

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