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CYCLING WITH ADHD?

Women and their hormones across the reproductive cycle

A few years ago, the notion that ADHD existed in women was something new. We have known for some time that ADHD appears to be far more common in boys than girls, but when this ratio is examined more closely, it appears the difference in prevalence depends on the sample studied. For example, in epidemiological samples, the female-to-male ratio is 1:3; and in clinical samples, the female-to-male ratio is between 1:5 to 1:9. Immediately, this striking difference raises questions about who is diagnosing and why so many girls are being missed?

Moving into adulthood, the prevalence and characteristics of ADHD in women has been similarly neglected in clinical practice and research. A worldwide meta-regression analysis of 11 studies of adults with ADHD found that although the differences in the ratio of boys to girls with ADHD decreased with age, women were still less likely to be diagnosed as adults. The ratio of 1:1.6 (females to males) was present in adults aged ≥19 years. Hence more men were being diagnosed in adulthood than women. Do these differences in diagnosis reflect a true variation in prevalence? Do divergent patterns exist for women and men when referred to the clinic for diagnosis and treatment? Does ADHD present differently in men and women and how does this contribute to diagnosis rates? These questions remain to be fully clarified.

Moving into adulthood, the prevalence and characteristics of ADHD in women has been similarly neglected in clinical practice and research. Recently, a worldwide meta-regression analysis of 11 studies of adults with ADHD found that although the differences in the ratio of boys to girls with ADHD decreased with age, women were still less likely to be diagnosed as adults. The ratio of 1:1.6 (females to males) was present in adults aged ≥19 years. Hence males still predominated. Whether these differences in diagnosis reflect a true difference in prevalence, differences in referral to the clinic for diagnosis and treatment or presentations remain to be clarified.

One of the intriguing new areas of research is how hormonal fluctuations throughout the reproductive cycle affect ADHD symptoms. With the background of differences in ADHD prevalence across the sexes, it is interesting to dig deeper into the physiology of the hormone fluctuations and how they impact on ADHD. This is the main focus of this paper.

To begin with the role of oestrogens: they affect the development and aging of brain regions that are crucial to higher cognitive functions, like verbal memory. There is increasing

evidence from in vivo brain imaging studies that oestrogen modulates cognitive function and cerebral blood flow, and promotes the release of monoamines in the brain. On a cellular level, recent literature shows that sex hormones may regulate intracellular signalling systems. Molecules involved with synaptic plasticity and neurotransmitter systems within the neuron that are implicated in ADHD may interact with oestrogens and therefore may explain some of the clinical characteristics of women with ADHD.

Critical to ADHD in women, oestrogens interact with the dopaminergic system, and therefore indirectly modulate executive functions, such as working memory and reward processing, as well as other aspects of cognitive functioning and mood. In contrast, low oestrogen can trigger greater irritability and disruptions of mood, sleep, and concentration.

In children with ADHD, there is some interesting research on the expression of certain oestrogen receptors and their role in the expression of ADHD symptoms, namely, the G-protein coupled oestrogen receptor (GPER). A recent study investigating serum oestrogen and GPER levels in children with ADHD reported comparable serum oestrogen levels but *reduced* GPER in ADHD children.

With the onset of menstruation, the reproductive hormones rise and fall in a monthly pattern. During the first two weeks of the menstrual cycle, the follicular phase, oestrogen levels rise steadily, while progesterone levels are low. This rise in oestrogen promotes serotonin and dopamine function, reducing ADHD symptoms. After ovulation, in the third and fourth weeks of the menstrual cycle, progesterone levels rise, and the beneficial effects of oestrogen diminish. Hence during the luteal phase, ADHD symptoms may worsen. In addition to greater irritability and low mood, a reduction in oestrogen may worsen concentration.

Puberty has other effects on girls with ADHD. According to the consensus statement by Young et al., puberty has been highlighted as a phase of high risk for mental health problems. The developmental changes that occur during puberty and later in adolescence may lead girls with ADHD to be particularly psychologically vulnerable if they are not able to access support.

In young women, fluctuating oestrogen levels may also influence the effectiveness of stimulant medications. A small study in 16 healthy women by Justice et al. showed that the effects of dextro-amphetamine (15 mg orally) were greater during the follicular phase than the luteal phase. During the follicular phase, subjects reported feeling more "high", "energetic and intellectually efficient" after taking dextro-amphetamine than during the luteal phase. While oestrogen seems to aid in the effectiveness of stimulants, progesterone likely decreases it (1999). These results were replicated by another small study showing that oestrogen and progesterone levels may impact on the subjective euphoric and stimulating effects of d-amphetamine in healthy women who are not affected by ADHD.

These findings suggest that oestrogen may enhance the subjective responses to a stimulant drug in women, but that this effect may be masked in the presence of progesterone.

Another study of young adult women (M_{age} = 20.2 ± 1.7 years) found that early menarche was associated with elevation in ADHD symptoms, including difficulties in attention, emotion regulation and more risk-taking behaviour, highlighting the potential impact of sex hormones on ADHD symptom profiles. Another study showed that high trait impulsivity in young adult women is particularly sensitive to decreased levels of oestrogen and raised progesterone, linking the reproductive cycle to a particular ADHD symptom.

Later on in their reproductive life, it appears that women with ADHD are more likely than controls to suffer from PMDD, post-natal depression and menopausal symptoms. Indeed, according to a recently published paper by Dorani et al, the prevalence of PMDD, PPD and climacteric scores were high in women with ADHD (2021).

A contributing reason to why women affected by ADHD may be at higher risk of postpartum depression is because they are more likely to have comorbid mood and anxiety disorders becoming pregnant. We know that comorbidity is the rule and not the exception in ADHD.

In contrast to these findings, higher circulating oestrogens appear to improve ADHD symptoms during pregnancy.

When oestrogen levels drop, during the perimenopause and menopause, women with ADHD may also have additional difficulties. Dropping oestrogen levels promote a drop in dopamine levels, which are already low in the brain affected by ADHD. Although there are several symptoms associated with perimenopause and menopause, two in particular are common for women affected by ADHD: changes in mood, primarily depression and anxiety, and increased inattention.

Prelimary studies have shown that women with ADHD are more likely to suffer from age-related cognitive changes, confusion, memory, concentration, and sleep disorders post-menopause.

Hence across the life cycle, evidence is accumulating that reproductive hormones play a role in the experience of women with ADHD. Although this research is only the beginning, it is critical to explore the impact of hormonal cycles on ADHD symptoms so that ultimately, girls and women with ADHD can be recognised, diagnosed and treated, with all attention to all phases of life.

References available upon request