Current research on the background of PMS and PMDD.

The reference list (including downloadable full text versions of the references) is to be found at the URL: http://www.medref.se/sidor/pms.html

1. It is now evident that progesterone metabolites constitute the main cause of the PMS syndrome. They are also, in sensitive women, responsible for the development of PMDD.

It is necessary to understand that the kind of **depression** in women with PMDD is different from the more common "endogenous" depression. Even though SSRI preparations can be used to ameliorate both, PMDD can be treated with discontinuous intake of the preparations in low dosages. This makes the adverse effects of SSRI much less important to consider.

2. Allopregnanolone (one of the metabolites of progesterone) is a neuroactive steroid with contradictory effects. Anaesthetic, sedative, and anxiolytic **as well as** aggressive and anxiogenic properties have been reported. A **bimodal association** between allopregnanolone concentration and adverse effects on mood has been observed.

3. It has been shown that progesterone-metabolites cause their negative mood changes through an action via the GABA-receptor. But this action is not consistent – a "tolerance development" has been described as a result of prolonged exposure to GABA-agonists. This is for example the case in endogenous rise in allopregnanolone concentration during prolonged stress situations and during pregnancy. The tolerance development is also prominent after periods of exogenous gestagen treatment.

4. To understand progesterone-induced adverse mood effects, it is important to note that progesterone is to a high degree metabolized to both allopregnanolone and and pregnanolone, both of which act as agonists on the GABA-A receptor complex in the brain. The GABA transmitter system is the major inhibitory system in the CNS. When GABA (gamma-amino-butyric acid) binds to the GABA-A receptor, the influx of chloride ions increases, hyperpolarizing the postsynaptic membrane and making the postsynaptic cell less prone to excitation.

Allopregnanolone is a GABA-A receptor positive modulator and enhances the effect of GABA on the receptor. The behavioral and pharmacological characteristics are **similar to those of ethanol, barbiturates, and benzodiazepines**.

5. Recent reports from human studies indicate that in certain individuals all the mentioned GABA-A receptor agonists can induce negative symptoms with anxiety, irritability and/or aggression. Strong influence is present in 3–6% of individuals while moderate symptoms are induced in 20–30%. **Interestingly enough, this parallels the 3–8% prevalence of PMDD among women in reproductive age and the 25–35% prevalence of milder PMS symptoms.**

6. Recent research work has also included the amygdala structure of the brain in the discussion. Progesterone (and its metabolites) seems to selectively increase amygdala reactivity in women. The amygdala is involved in a wide range of emotional behavior, including social cognition and the stress response – all of which appears to be modulated by progesterone. One example is the enhancement of the response of the hypothalamus–pituitary–adrenal (HPA) axis to stressors during the luteal phase.

7. The currently **increased** knowledge might be summarized as follows:

Depression and anxiety often affect women in relation to reproductive events like menarche, premenstrual periods, post-partum and around menopause. Sex and stress hormones are metabolized to neuroactive steroids with effects on brain function as modulators of the GABA-A receptor similar to benzodiazepines, barbiturates and alcohol. One example of a strong neuroactive sex steroid is allopregnanolone.
One of the more noticeable examples of the interaction between mood, neuroactive-steroids and the GABA system is the premenstrual dysphoric disorder (PMDD).

GABA-steroids, other than from progesterone origin, are produced within the brain, by the adrenals at stress and from the ovary during the menstrual cycle. Studies have shown that all these have a **bimodal effect** on behavior. In high dosages (or concentrations) the GABA-A receptor modulators are **CNS depressants, anesthetic, and anxiolytic**. But in **low concentrations –** and especially in sensitive individuals **– instead of being anxiolytic they cause severe anxiety, irritability, aggressiveness and depressive mood**.

8. An international committee has been formed in order to discuss criteria for PMS and PMDD that will become widely accepted. The committee members verbalize themselves as follows:

“The prevalence of PMS, its personal and public health impact combined with the burden of disease call for uniform and widely accepted definitions and diagnostic criteria. In the report of an international multi-disciplinary consensus group, such criteria are recommended. The criteria emphasize timing, impairment and distress, and allow for subtypes of PMS to emerge. It is hoped that specified quantifications will allow for **improvement in targeted clinical trials,** increased understanding of underlying mechanisms of specific symptoms, as well as culturally sensitive comparable studies of epidemiology and burden of disease.”

9. At the same time as fundamental research is going on, a group of Japanese researchers publishes two papers describing very specific methods to register autonomic nervous system activity in the late luteal phase. They are assessing the nervous activity by means of “heart-rate variability (HRV) power spectral analysis” in three groups, a control group, a PMS group and a PMDD group. Even though their discussion is interesting, their methodology is far from international acceptance. They also suggest the altered autonomic nervous system activity as a “potential etiological factor” of the PMS syndrome rather than understand that it is barely a consequence of the response of the central nervous system to the neuroactive metabolites of progesterone.

The Japanese group, in a third paper, reports lower peripheral circulation in young women with premenstrual symptoms. They use another, not widely known monitoring device, by which “venous oxygenation index” (VOI) can be calculated based on the ratio of light absorption of oxyhemoglobin and deoxyhemoglobin. The group demonstrates their sincere endeavor to find diagnostic criteria for PMS and PMDD that could be added to the existing ones.

I fully agree with professor O’Brien, saying: "If the newly published (Japanese) work will prove to be clinically useful, it might have the potential at least to provide a relatively non-invasive method to distinguish women with PMS from those who have different non-hormonal types of mood disorder."

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