Pathways to Lifelong Mental Wellbeing
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# Hormones and Mood

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## Background

Women of reproductive age represent approximately 50% of the worldwide female population and 25% of the total population. Hormonal variations characterize crucial phases in a woman´s life, such as the menstrual cycle, pregnancy and postpartum, as well as the menopausal transition. These are acknowledged windows of vulnerability for mental disorders in women. As clinicians and researchers, we constantly meet female patients, women, journalists, and opinion-leaders who are shocked at the knowledge gaps surrounding women's mental health, especially at some of the most valued and treasured time points in their life. Within the open space of this workshop, we discussed the relevance of hormonal contraception, premenstrual dysphoric disorder, peripartum depression, and hormonal replacement therapy in relation to mental wellbeing.

## Approach

The goal was to generate questions, ideas or suggestions that can support policies promoting women's mental wellbeing. Specifically, the workshop sought to foster awareness of the challenges that accompany the reproductive lifespan as well as to support the development of targeted research and care for those women who react maladaptively to the hormonal fluctuations experienced in connection with the menstrual cycle, pregnancy and postpartum, and the menopausal transition. Dr. C. Neill Epperson's inspirational talk highlighted that women make up half of the world's population, gestate and nurture future generations, and make the vast majority of healthcare decisions for their families. Hence, improving women's health should be a major focus of public health across the globe. This initiated the general discussion about considering the issue in its entirety. Topic-specific overviews – including the perils and pitfalls of hormonal therapy (i.e., hormonal contraceptives or hormonal replacement therapy) and sex-specific psychiatric disorders (i.e., peripartum depression and premenstrual dysphoric disorder) – were then addressed:

- When combined oral contraceptives were introduced in the 1960s, women gained the ability to control their fertility and to separate sexual intercourse from reproduction. Today, there is a wide range of hormonal contraceptives available, with different routes of administration and various doses of progestogens and oestrogens. Apart from contraception, hormonal contraceptives provide additional health benefits such as decreased menstrual bleeding and amelioration of menstrual pain. Although hormonal contraceptives have been on the market for decades, several questions concerning their effect on mood still exist. Previous observational studies have suggested that hormonal contraceptive use may be associated with both improvement and deterioration, thus no consistent findings are at hand. Randomized controlled trials have suggested that some women do deteriorate while receiving hormonal contraceptive treatment, but the effect sizes are generally small and the clinical relevance is unclear. In recent years, however, some register-based observational studies have found an association between use of hormonal contraceptives and subsequent depression among adolescents, at least regarding non-oral preparations such as the vaginal ring and the hormonal intrauterine device. The risk decreases when adjustments for medical indication for hormonal contraceptives use (such as acne and dysmenorrhea) are made, but they still remain. There may be residual confounding factors among adolescents using hormonal contraceptives that are themselves independent risk factors for depression, but that are not captured using this type of study design. However, it is also possible that the maturing young brain is more sensitive to exogenous steroid hormones, at least during the teenage years.

- Notably, menstrual-cycle-related hormonal fluctuations are negatively experienced by ~1.7 billion women of reproductive age in the world. Maladaptive brain sensitivity to these changes likely leads to the severe psychological, cognitive, and physical symptoms repeatedly experienced by women with Premenstrual Dysphoric Disorder (PMDD) during the late

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luteal phase of the menstrual cycle. Indeed, 5-8% of menstruating women suffer from PMDD. PMDD is distinguished by symptoms such as depressed mood, anxiety, emotional lability and irritability, which peak during the days immediately preceding menstruation. Patients suffering from PMDD experience these symptoms to such an extent that they interfere with their ability to perform socially, at work and at home. Importantly, many more women experience sub-clinical forms of PMDD that are impairing their daily functioning, often described as premenstrual syndrome (PMS). Despite the prevalence and the fact that this burden may affect women for a period of several years up to decades during their fertile age, our knowledge about the neurobiology and treatment of PMDD and PMS are rather limited.

- Another challenging period in a woman's life is pregnancy and the postpartum phase, which represent not only physiologically but also psychologically extraordinary events. Major depressive disorder at the time of childbirth, or peripartum depression(PPD), affects about 10% of all newly delivered women and has implications for the mother, the family, and not least, the child´s neurodevelopment. Likely triggered by hormonal sensitivity in interaction with psychosocial factors, PPD is rarely spoken of, possibly because it is considered particularly shameful to develop a depressive disorder at this stage of life, and afflicted women are reluctant to seek medical care for their symptoms. Moreover, the growing foetus must be given extra consideration when discussing treatment options, adding to the challenges of managing these patients. From a clinical perspective, peripartum depression is thus an under-diagnosed and under-treated disorder with sometimes devastating consequences. Despite several plausible pathophysiological pathways for disease development, due to the extreme hormonal and immune system fluctuations during and after childbirth, to date there are no clinically applicable biomarkers of any kind available for PPD.

- Later in life, the menopausal transition, which can last for several years, is the most influential biological and health-related event for most middle-aged women. Indeed, peri- and post-menopause are marked not only by vasomotor symptoms, but also by cognitive and mood complaints that affect the quality of life and overall functioning of women. Additionally, deciding whether or not to use hormonal replacement therapy therapy continues to be a point of some debate among clinicians caring for mid-life women.

Following these topic-specific presentations on the state of the art, the participants focused on the perils and pitfalls of hormonal contraception. While billions of women are prescribed hormone therapy to regulate their menstrual cycle and to control their fertility, the impacts on the woman´s mental and reproductive functions – including stress, mental health, quality of life, sexual functioning, and effects on brain and behaviour – are poorly known. The participants, national and international experts (including health-care professionals, scientists from academia, and the pharmaceutical industry), contributed by sharing their perspectives on the question: "Can birth control pills lead to an increased risk of depression for women?". The main conclusion was that the majority of women should not expect to experience adverse mood due to hormonal contraceptive use. Clearly, advanced knowledge about the determinants of exogenous hormonal treatment in women is needed. Moreover, because young women (12-16 years) who discontinue use of an effective contraceptive are at increased risk of an unwanted pregnancy, the importance of investigating whether, and why, adolescents may be more vulnerable to developing hormonal contraceptive-induced adverse mood was stressed.

## Recommendations

Women's health, particularly women's mental health, is an extremely under-researched area that has suffered for years from a lack of systematic biological and psychosocial approaches, thus impeding the development of sex-specific prevention, screening and treatment. At the same time, depressive disorders, such as premenstrual dysphoric disorder and peripartum depression, affect large proportions of the female population during their reproductive and most productive years, at a societal cost that exceeds the costs posed by Alzheimer's disease, cardiovascular disease, diabetes, and cancer.

- First, men can no longer be the standard in biomedical research (e.g., drugs should also be tested in women, women should be represented in research studies, and the effect of sex should be adequately assessed statistically). This can be achieved through an understanding of sex-specific differences in mental health and illness.

- Second, the hormonal and reproductive state matters for medical and scientific assessment (e.g., there are sex differences and profound hormonal fluctuations across the life cycle and within the menstrual cycle). The wellbeing of women who are sensitive to hormone fluctuations should be investigated in relation to aging and lifestyle factors, as they are likely to impact mental outcomes. Screening to identify vulnerable women should be implemented and harmonization of specialized advice should be supported (e.g., to discuss mood problems associated with hormonal contraceptive use without discouraging women, to consider the risk-benefit trade-off of abortion, absence of side effects, positive health benefits, premenstrual syndrome, acne, endometriosis, and the risk of side effects associated with PMS, but without polarizing the discussion).

- Third, ways to ensure the health of women within a personalized, precision medicine framework need to be promoted. It is important to support the development of targeted research and care for women who react maladaptively to hormonal fluctuations experienced in connection with the menstrual cycle, pregnancy and postpartum, and the menopausal transition (e.g., to define the medical responsibility for women-specific neuropsychiatric disorders through collaborative and communicative actions between clinical expertise; to tackle therapy resistance or non-adherence through women-specific follow-up assessments; and to adjust prescription based on reaction; to diminish erroneous and delayed diagnosis by promoting dialogue between the research community, social welfare and healthcare providers). Moreover, reconciling research with actual clinical knowledge is needed.

- Lastly, and particularly relevant within sociocultural environments characterized by taboos and stigma on women's mental health, the dissemination of our understanding of specific reproductive epochs as sensitive phases (e.g., involvement of social influencers to reduce stigma), awareness of the impact of hormones on women (e.g., campaigning against misinformation on the internet), and facilitation of treatment-seeking behaviour (e.g., to generate outreach for research and for the subject via the media), are potential strategies that could reduce the knowledge gap on women´s mental health.

In conclusion, the following recommendations represent a call to action to advance "sex/gender equality" in everyday life and in healthcare. Notably, the following questions should be the subject of dedicated strategical multidisciplinary programmes intended to foster better global health. How can we build fruitful collaborations between scientists, governments, non-governmental organizations, and companies to find long-lasting solutions? What are the challenges? How can we work together to meet the needs of women? How can we encourage companies to support the development of therapies and services? How can we reduce stigma, discrimination, exclusion, and poor health, and improve appropriate healthcare? From this perspective, joint efforts between academia, the social welfare and healthcare sector, and policymakers are needed to advance women´s wellbeing worldwide.

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