Hormonal contraceptive designs and women's mental health – Timing is of the essence!

openaccessgovernment.org/article/hormonal-contraceptive-designs-and-womens-mental-health-timing-is-of-the-essence/186141

9 December 2024

Professor Belinda Pletzer from the Centre for Cognitive Neuroscience at Paris Lodron University of Salzburg explores the physical and psychological symptoms of a pill pause. She advocates for hormonal contraceptive designs that focus on women's health needs instead of socio-cultural misconceptions about menstrual bleeding

Traditionally, combined oral contraceptives (COCs, aka 'the pill') follow a 21+7-day intake cycle, where a 21-day intake period is followed by a 7-day pill pause, alternatively mimicked by a 7-day placebo pill phase. The majority of COCs on the market still follow this cyclic intake regime, although the number of formulations approved for continuous use, as well as off-label continuous use of COCs, is increasing.

Many women are convinced that the pill pause is a medical necessity to avoid the adverse effects of cumulative hormone doses. However, research comparing the adverse effects of continuous intake to cyclic intake is only slowly accumulating. Instead, the pill pause is a historic artefact, given that the first contraceptive pill, Enovid, was – for social, cultural, religious, or political reasons outside the scope of this article – first approved for menstrual cycle regulation rather than contraception. To mimic a 'natural' menstrual cycle, women had to bleed at regular intervals. The pill pause is effectively a period of hormone withdrawal and thus stimulates withdrawal bleeding in the majority of women. Therefore, the question of whether or not to pause during COC use translates into the question of whether or not women have to bleed. And who gets to decide when and if they do?

The first pill designed for continuous intake (Lybrel) was approved in 2007, almost 50 years after Enovid entered the market. Since then, continuous intake has increased and is particularly recommended for endometrioses and dysmenorrhea. [(1)] However, misconceptions about the physiological grounds for the pill pause still prevail. While the withdrawal bleeding may look like a normal period from the outside, it is not comparable to menstruation for various reasons – the simplest being the lack of ovulation during COC use. Thus, withdrawal bleeding is not a biological requirement!

The pill pause from a mental health perspective

What is often overlooked is that for a certain percentage of women, periods of hormone withdrawal come with a number of physical and psychological side effects like headaches, bloating and menstrual pain, or depression, anxiety, irritability, and mood swings. 3-8% of women suffer from premenstrual dysphoric disorder (PMDD), with about

20% reporting a milder form of premenstrual syndrome (PMS). [2] However, while an increasing number of studies research natural hormone withdrawal periods, as well as adverse effects associated with active pill intake, the question of adverse effects associated with synthetic hormone withdrawal during the pill pause is rarely addressed.

In a recent study, we demonstrated that mental health symptoms typically associated with the premenstrual phase increase, on average, by 24% during the pill pause. [3] The effect size was comparable to the average increase in mental health symptoms during menstruation in a group of naturally cycling women, as was the variability in symptom changes across women. Thus, while the physiological grounds of the withdrawal bleeding may differ from menstruation, the effects of the hormone withdrawal on the brain appear similar. Therefore, it is unsurprising that results regarding the effectiveness of COCs in treating PMS and PMDD are highly inconsistent. [4] Women who experience psychological symptoms during endogenous hormone withdrawal can be expected to keep experiencing those symptoms during synthetic hormone withdrawal.

Notably, the symptoms during the pill pause were irrespective of the contraceptive formulation, i.e., not dependent on progestin type or estrogen dosage. Thus, while side effects during active intake of hormonal contraceptives are often moderated by progestin type and estrogen dose, withdrawal symptoms were not. However, a commonality between symptoms experienced during active intake and the withdrawal phase is that symptoms were stronger in women with higher trait depression or a history of mental health problems. [3, 5] Thus, from a mental health perspective, continuous use is preferable to cyclic use, especially for women with a history of PMS or PMDD.

The pill pause from a blood flow perspective

This clear recommendation for continuous use drawn from a psychological viewpoint raises the question of whether it is safe to do so from a physical point of view. This question deserves special attention, particularly due to the strong belief among women that the main reason for the pill pause is to reduce side effects. Like psychological symptoms, physical symptoms associated with hormone withdrawal, like headaches or menstrual pain, disappear with continuous use. [1] Breakthrough bleedings occur more commonly with continuous than cyclic intake. While these are not concerning from a health perspective, users may perceive them as disruptive. To avoid unscheduled bleedings, users prone to breakthrough bleedings may prefer short scheduled pill pauses of 3-4 days at an individual frequency. However, data also demonstrate that breakthrough bleedings decline over the first year of continuous use. [1]

The most concerning side effect to be considered with any hormonal contraceptive is venous thromboembolisms, i.e., blood clots. Thrombosis risk varies between contraceptive formulations with lower risks associated with lower estrogen doses, bioidentical estrogens as opposed to ethinylestradiol, and androgenic progestins like levonorgestrel compared to anti-androgenic progestins like drospirenone. [6] Regarding the risk of thrombosis in relation to the timing of intake and intake schemes, less data are available. On the one hand, the risk of blood clots seems to increase during the first year

of intake and stabilize thereafter. [7] On the other hand, studies suggest that the continuous intake scheme is associated with a 1.4 times increased risk for blood clots as opposed to cyclic regimens. [8] However, given that the risk varies between sub-populations and formulations available for continuous and cyclic use are not entirely comparable regarding dosages, the clinical relevance of these findings is still debated. It is also important to note that the risk is still very low in healthy young women without a family history of thromboembolism.

In summary, the issue of the pill pause nicely outlines two major challenges in hormonal contraceptive designs. First, benefits and side effects may depend on temporal aspects like the timing, duration, and frequency of intake as on the specific formulation. This aspect needs to be explored for all contraceptive formulations available. Second, with the COCs currently available, there appears to be a trade-off between mitigating the risks for mental health effects and venous thromboembolism. Thus, there is an urgent need for new hormonal contraceptive designs that address these challenges and are driven by the health needs of women rather than by socio-cultural misconceptions about when and how often women are supposed to bleed.

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- OAG 045 - January 2025

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