

# Brain Effects of CONTRAceptives in long-term hormonal contraceptive users

DDr Belinda Pletzer and  
 Dr Isabel Noachtar

At a time when women's reproductive rights face renewed controversy, safe and reliable contraceptive options are of grave importance. However, while various hormonal contraceptive options are available, data regarding their risks and benefits on mental health are either lacking or inconsistent and thus subject to miscommunication, which is confusing for women.

Due to these concerns, many women are either reluctant to start hormonal contraceptive treatment for fear of potential side effects or may discontinue hormonal contraceptive use for fear of potential long-term effects (Pletzer *et al.*, 2022). The BECONTRA project accompanies first-time and long-term users of hormonal contraceptives over several months to assess potential effects on the brain, emotion and cognition. At this stage of the project, we can present first results on long-term oral contraceptive users who tolerate their pill well.

## Mental health and hormonal contraceptive use – disentangling the scientific evidence

Of particular concern for hormonal contraceptive users are mental-health-related side effects. However, large-scale studies from different countries report either an increase in mental health problems like depression or suicide (e.g. Skovlund *et al.*, 2016, 2018), no change in mental health problems (e.g. Lundin *et al.*, 2022) or a decrease in mental health problems during hormonal contraceptive use (e.g. Keyes *et al.*, 2013; Cheslack-Postova *et al.*, 2015). While these data may seem inconsistent at a first glance, it is important to view them from a more individualised perspective (Lundin *et al.*, 2021).

While some women may experience adverse effects of hormonal contraceptives on their mental health, others may profit from mood-stabilising effects of hormonal contraceptives. Adverse mood effects usually become apparent during the first few months of contraceptive treatment, and women who experience such adverse mood effects often discontinue hormonal contraceptive treatment (Poromaa and Segebladh, 2021). They are thus not equally represented in all studies on hormonal contraceptive users. Studies focusing on the first few months of hormonal contraceptive use are thus more likely to detect a mood worsening (Lundin *et al.*, 2017).

On the other hand, women who tolerate their pill well are more likely to be represented in studies on long-term hormonal contraceptive users (Keyes *et al.*, 2013; Cheslack-Postova *et al.*, 2015). Raising awareness for these individualised responses and adequately communicating the generalisability of hormonal contraceptive research results is of utmost importance. This is crucial to adequately address the mental health concerns of women who experience adverse mood effects while not discouraging women who tolerate hormonal contraceptives (Petersen *et al.*, 2023).

## Long-term hormonal contraceptive use, what are the issues?

If women tolerate their pill well, they may continue hormonal contraceptive treatment for several years. During this time, they are faced with three questions that hormonal contraceptive research needs to address:

1. To pause or not to pause? What happens during the pill-free interval?
2. Are there accumulative effects of hormonal contraceptive use over time?
3. Are the effects of long-term hormonal contraceptive use reversible?

In the BECONTRA project, we have addressed these questions via three approaches. First, to assess how mood and cognition change during the pill-free interval, we have studied long-term hormonal contraceptive users during their pill pause compared to active intake. Second, to assess accumulative effects, we have correlated hormonal contraceptive treatment duration with different aspects of mood, cognition and their neural underpinnings. Third, to gain a first idea about the reversibility of hormonal contraceptive effects, we have studied those aspects related to contraceptive treatment in current users in association with previous contraceptive treatment duration.

## 1. What happens during the pill-free interval?

The most commonly used hormonal contraceptives on the market are combined oral contraceptives (COCs), colloquially summarised as 'the pill'. The majority of COCs adhere to a 'pill cycle' of 21–24 active days, followed by 4–7 inactive days, during which intake is paused or replaced by placebo pills. This intake pattern has been favoured in order to introduce COCs as a method for menstrual cycle control, resulting in regular bleeding patterns. However, while many women theoretically favour extended pill cycles without pill-free intervals (Sulak *et al.*, 2002), little information is available on how adverse and beneficial effects of COC use compare between interrupted and continuous intake.

We have made a first attempt to address this question from a mental health perspective and have compared mood and cognition between the active and inactive phases in 120 long-term users of COCs. The large sample and comparison to previous data on the menstrual cycle allowed us to also address whether changes were

- i. dependent on the contraceptive type,
- ii. dependent on trait depression,
- iii. comparable to changes in naturally cycling women along the menstrual cycle.

To assess mood, we used well-validated psychological instruments for

- i. anxiety,
- ii. negative affect,
- iii. mental health symptoms typically associated with the premenstrual phase, e.g. mood lability or irritability.

To assess cognition, we used standardised tasks of

- i. navigation,
- ii. mental rotation, and
- iii. verbal fluency.

The results demonstrate that—as in naturally cycling women—cognition doesn't change along the pill cycle (Noachtar and Pletzer, 2023), while mood worsens substantially during the pill pause, including a 7 percent increase in anxiety, 13 per cent increase in negative

affect, and 24 per cent increase in mental health symptoms (Noachtar *et al.*, 2023). These changes were irrespective of the COC type but more pronounced in women with higher trait depression (Noachtar *et al.*, 2023). From a mental health perspective, these data question the utility of the pill pause and highlight the urgency for more research into the risks and benefits of extended pill cycles with various contraceptive formulations.

It is presently unclear whether this mood worsening is a direct result of hormone withdrawal, e.g. due to changes in neurotransmitter levels, or mediated via the physical discomfort associated with the withdrawal bleeding. However, endogenous hormone withdrawal has been related to adverse mood symptoms in a variety of scenarios, including the premenstrual phase (premenstrual syndrome, premenstrual dysphoric disorder), the postpartum period (baby blues, postpartum depression), as well as menopause (peri-menopausal depression). The data also provide further evidence that women with a history of mental health problems are particularly vulnerable to developing adverse mood symptoms during periods of hormonal change. A history of depression has already been identified as a risk factor for adverse mood effects during the first few months of hormonal contraceptive treatment (Lundin *et al.*, 2021), which in turn has been identified as a risk factor for postpartum depression (Larsen *et al.*, 2023). Our data demonstrate that higher trait depression also increases the risk of experiencing adverse mood symptoms during the pill-free interval (Noachtar *et al.*, 2023). Together, these data highlight the importance of incorporating mental health aspects in obstetrics and gynaecology.

## 2. Do effects of long-term COC use accumulate over time?

While short-term hormonal withdrawal during the pill pause results in mood worsening but does not affect cognition, the opposite appears to be the case for accumulative effects. The pill use duration was unrelated to any aspect of mood or mental health. However, some

mild associations between the duration of pill use and cognition were observed (Noachtar *et al.*, 2022; Noachtar *et al.*, 2023). Longer duration of pill use was associated with slightly improved orientation accuracy during navigation (Noachtar *et al.*, 2023), a shift in the strategy used during word production in the verbal fluency task (Noachtar *et al.*, 2022; 2023), as well as some alterations in the processing of novel faces (Pletzer *et al.*, 2022). These changes in behaviour were also associated with changes in the underlying neural correlates (Noachtar *et al.*, 2022; Pletzer *et al.*, 2022). Longer duration of pill use was associated with changes in the way key brain areas for navigation (i.e. the hippocampus or caudate nucleus), verbal fluency (i.e. the inferior frontal gyrus) or face processing (i.e. the fusiform face area) connected with other brain areas. These associations to brain connectivity hint at changes in the way the environment, verbal information or faces are represented in the brain. Interestingly, these associations were comparable for all pill types in navigation and verbal fluency but depended on the type of pill used for face processing. Importantly, apart from orientation accuracy during navigation, all associations to the duration of pill use were indicative of a strategy shift rather than overall performance measures. The fact that changes in the brain were mostly reflected at the level of brain connectivity supports this notion and provides further evidence that the female brain is capable of efficiently adapting the way information is processed to changes in the hormonal milieu.

## 3. Are effects of long-term hormonal contraceptive use reversible?

While true reversibility can only be determined if women are studied for several years after discontinuation of COC use, we used the previous contraceptive treatment duration of women who had discontinued COC use prior to the study to obtain a first idea of whether associations to previous contraceptive use would still be visible in the brain after discontinuation. The duration of previous COC use was not related to the majority

of measures associated with current COC use. For example, neither navigation performance nor its neural underpinnings were related to how long women had previously used the pill (Noachtar *et al.*, 2022). Also, neither verbal fluency performance nor face processing were related to how long women had previously used the pill, and neither were the majority of their neural correlates (Noachtar *et al.*, 2022; Pletzer *et al.*, 2023). One exception was a higher activation of the putamen in women with longer previous contraceptive use (Noachtar *et al.*, 2022), which is in line with previous findings of larger putamen volumes in women with longer previous contraceptive use (Pletzer *et al.*, 2019). However, putamen volume was also smaller the longer the time-point of discontinuation had passed (Pletzer *et al.*, 2019), suggesting that for some selected brain parameters, it might just take longer to eliminate all traces of previous contraceptive use. Nevertheless, extensive follow-up in longitudinal studies, underway in the BECONTRA project, is required before any definitive conclusions can be drawn from these latter findings.

## Summary

In summary, these results represent good news for long-term hormonal contraceptive users. While there were some associations of longer treatment duration with cognitive parameters, these associations were small, reflected strategy shifts rather than overall performance changes and could not be confirmed after discontinuation of hormonal contraceptive treatment. The duration of use was also not related to mood or mental health. Most importantly, a mood worsening was observed during the pill pause, comparable to the change they could expect to experience during menstruation if they were not on the pill. However, the results during the pill pause warrant more research into the benefits of alternative intake schemes, like extended pill cycles or continuous usage. If women experience a mood worsening during their pill pause, they may want to consult with their doctor about adjusting their pill cycles.



## References

- Cheslack-Postava, K., Keyes, K. M., Lowe, S. R. and Koenen, K. C. (2015) 'Oral contraceptive use and psychiatric disorders in a nationally representative sample of women', *Archives of Women's Mental Health*, 18, pp. 103–111.
- Keyes, K. M., Cheslack-Postava, K., Westhoff, C., Heim, C. M., Haloosim, M., Walsh, K. and Koenen, K. (2013) 'Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States', *American Journal of Epidemiology*, 178(9), pp. 1378–1388.
- Larsen, S. V., Mikkelsen, A. P., Lidegaard, Ø. and Frokjaer, V. G. (2023) 'Depression Associated With Hormonal Contraceptive Use as a Risk Indicator for Postpartum Depression', *JAMA Psychiatry*, 80(7), pp. 682–689.
- Lundin, C., Danielsson, K. G., Bixo, M., Moby, L., Bengtsdotter, H., Jawad, I., Marions, L., Brynhildsen, J., Malmborg, A., Lindh, I. and Poromaa, I. S. (2017) 'Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle—a double-blind, placebo-controlled randomized trial', *Psychoneuroendocrinology*, 76, pp. 135–143.
- Lundin, C., Wikman, A., Bixo, M., Gemzell-Danielsson, K. and Poromaa, I. S. (2021) 'Towards individualised contraceptive counselling: clinical and reproductive factors associated with self-reported hormonal contraceptive-induced adverse mood symptoms', *BMJ Sexual & Reproductive Health*, 47(3), e1-e8.
- Lundin, C., Wikman, A., Lampa, E., Bixo, M., Gemzell-Danielsson, K., Wikman, P., Ljung, R. and Sundström Poromaa, I. (2022) 'There is no association between combined oral hormonal contraceptives and depression: a Swedish register-based cohort study', *BJOG: An International Journal of Obstetrics & Gynaecology*, 129(6), pp. 917–925.
- Noachtar, I. A., Hidalgo-Lopez, E. and Pletzer, B. (2022) 'Duration of oral contraceptive use relates to cognitive performance and brain activation in current and past users', *Frontiers in Endocrinology*, 13, 885617.
- Noachtar, I. A., Frokjaer, V. G. and Pletzer, B. (2023) 'Mental Health Symptoms in Oral Contraceptive Users During Short-Term Hormone Withdrawal', *JAMA Network Open*, 6(9), e2335957–e2335957.
- Noachtar, I. A. and Pletzer, B. (2023) 'Spatial and Verbal Performance relates to the Duration of Combined Oral Contraceptive Use, but does not change during the Pill-free Interval', *PsyArxiv*: <https://psyarxiv.com/j4e6w/>
- Petersen, N., Beltz, A. M., Casto, K. V., Taylor, C. M., Jacobs, E. G., Sundström-Poromaa, I. and Pletzer, B. (2023) 'Towards a more comprehensive neuroscience of hormonal contraceptives', *Nature Neuroscience*, 26(4), 529–531.
- Pletzer, B., Harris, T. and Hidalgo-Lopez, E. (2019) 'Previous contraceptive treatment relates to grey matter volumes in the hippocampus and basal ganglia', *Scientific Reports*, 9(1), 11003.
- Pletzer, B., Lang, C., Derntl, B., and Griksiene, R. (2022) 'Weak associations between personality and contraceptive choice', *Frontiers in Neuroscience*, 16, 898487.
- Pletzer, B., Noachtar, I. and Hidalgo-Lopez, E. (2023) 'Hormonal contraception & face processing: Examining face gender, androgenicity & treatment duration', *Psychoneuroendocrinology*, 154, 106292.
- Poromaa, I. S. and Segeblad, B. (2012) 'Adverse mood symptoms with oral contraceptives', *Acta Obstetrica et Gynecologica Scandinavica*, 91(4), pp. 420–427.
- Skovlund, C. W., Mørch, L. S., Kessing, L. V. and Lidegaard, Ø. (2016) 'Association of hormonal contraception with depression', *JAMA Psychiatry*, 73(11), pp. 1154–1162.
- Skovlund, C. W., Mørch, L. S., Kessing, L. V., Lange, T. and Lidegaard, Ø. (2018) 'Association of hormonal contraception with suicide attempts and suicides', *American Journal of Psychiatry*, 175(4), pp. 336–342.
- Sulak, P. J., Kuehl, T. J., Ortiz, M., and Shull, B. L. (2002) 'Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms', *American Journal of Obstetrics and Gynecology*, 186(6), pp. 1142–1149.

## PROJECT NAME BECONTRA

### PROJECT SUMMARY

The ERC Starting Grant project “How birth control pills affect the female brain (BECONTRA)” intends to characterise neuronal, emotional and cognitive effects of COC treatment and its reversibility upon withdrawal in a longitudinal design. The effects will be compared between the most commonly used contraceptives and between adolescent and adult COC users.

### PROJECT LEAD PROFILE

Born in Austria, Belinda Pletzer received two outstanding doctorates from Salzburg University. Her research focuses on the interactions between endocrine and nervous system with a specific focus on gender aspects and women's health. She authored over 80 articles, including the first study on the effects of birth control pills on the brain.

### PROJECT PARTNERS

The BECONTRA project is based at the Centre for Cognitive Neuroscience at the Paris-Lodron University Salzburg (PLUS) in close cooperation with the Department of Gynaecology at the Private Medical University (PMU) of Salzburg. Collaboration partners include groups from Germany, Sweden and beyond.

### CONTACT DETAILS

DDr Belinda Pletzer  
Hellbrunnerstr. 34, 5020 Salzburg, Austria

+43 662 8044 5184  
Belinda.Pletzer@sbg.ac.at  
<https://ccns.sbg.ac.at/people/pletzer>



### FUNDING

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under grant agreement No. 850953.