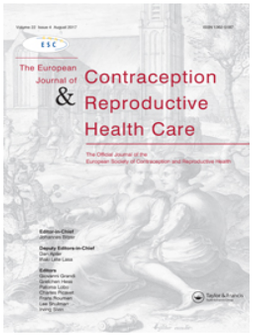

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The European Journal of Contraception & Reproductive Health Care

ISSN: 1362-5187 (Print) 1473-0782 (Online) Journal homepage: http://www.tandfonline.com/loi/iejc20

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To cite this article: G. S. Merki-Feld, D. Apter, G. Bartfai, G. Grandi, K. Haldre, M. Lech, R. Lertxundi, I. Lete, P. Lobo Abascal, S. Raine, F. Roumen, D. Serfaty, L. P. Shulman, S. Skouby & J. Bitzer (2017) ESC expert statement on the effects on mood of the natural cycle and progestin-only contraceptives, The European Journal of Contraception & Reproductive Health Care, 22:4, 247-249, DOI: 10.1080/13625187.2017.1353075

To link to this article: https://doi.org/10.1080/13625187.2017.1353075

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE, 2017
VOL. 22, NO. 4, 247–249
https://doi.org/10.1080/13625187.2017.1353075

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EXPERT STATEMENT

ESC expert statement on the effects on mood of the natural cycle and progestin-only contraceptives

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ABSTRACT

Hormonal fluctuations during the natural cycle, as well as progestins used for hormonal contraception, can exert effects on mood especially in vulnerable women. Negative effects of levonorgestrel-releasing intrauterine contraception on mood are rare.

ARTICLE HISTORY
Received 5 July 2017
Accepted 5 July 2017
Published online 21 July 2017

KEYWORDS
Depression; hormone-releasing intrauterine systems; mood variations in the natural cycle; progestin-only contraception

Hormonal contraceptives have attracted a lot of media attention in recent years, causing uncertainty and fear of adverse events among users and women seeking effective contraception. A recent article published in *Spiegel Online* claims that the low-dose 20 μg levonorgestrel-releasing intrauterine system (LNG-IUS 20 μg/d) potentiates stress reactivity and may exert mood alterations including depression, anxiety, nervousness and sleeplessness. The contents of the online article have been published in several European countries and have caused uncertainty among many users. The statement on increased stress reactivity is based on an article published in *Psychoneuroendocrinology* reporting increased cortisol levels in LNG-IUS 20 μg/d users in an experimental setting [1].

Contraception has never been as effective and safe as it is today. The broad choice of methods allows individual counselling adapted to each woman's health, personal situation and age. Before a hormonal contraceptive enters the market, its effects have been studied in at least 20,000 28-d cycles, corresponding to use among more than 1500 women over the course of a year. The study data provide very clear information about what may be expected with its use. The data do not indicate that the occurrence of any type of adverse event is close to zero, but provide reassurance that harmful adverse events are very rare.

In public discussions and press releases about rare side effects of hormonal contraceptives, it would improve general understanding of the message and prevent unfounded fears if the absolute number of events were quoted. Furthermore, informing the reader which women are vulnerable to a rare adverse event would lead the discussion in a more constructive direction. Unfortunately, however, most media articles do not discuss rare adverse events in relation to the main benefit of hormonal contraception, which is the prevention of unplanned pregnancies. On the other hand, press releases ensure that few women feel insufficiently informed about the potential side effects of a method. It is a major aim of the ESC to teach doctors how to conduct qualified and thorough counselling, through seminars, congresses and courses as well as via the online teaching tool. Some of the ESC's recommendations for tailored counselling are given at the end of this article and have previously been published in another context in a recent editorial in *The European Journal of Contraception and Reproductive Health Care* [2].

This article discusses three aspects of mood alterations in more detail:

- Mood effects occurring in the natural cycle.
- Mood effects of all three types of LNG-IUS and other progestin-only contraceptives.

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- Conclusions that may be drawn from the study reporting potentiated stress reactivity [1].

It is well known that hormones and their fluctuations in the natural cycle are frequently associated with mood alterations: 20% of women report premenstrual symptoms and 5% premenstrual dysphoric disorder (PMDD), which can lead to functional impairment and diminished quality of life comparable to that of a major depressive disorder. Interestingly, the prevalence of a lifetime psychiatric disorder in PMDD patients is 55%, suggesting a predisposition for a special interaction between the brain and hormones in this subset of women [3]. PMDD improves not only with use of antidepressants but also with use of the 20 μg ethinylestradiol/3 mg drospirenone combined oral contraceptive [4,5]. In the context of negative reports with regard to combined oral contraceptives and mood, this sort of finding in high-quality prospective studies emphasises how individual the reaction of mood to hormones can be. A typical situation in which natural hormones exert a negative effect on mood is in postpartum depression, which affects around 10% of women.

There has never been any doubt that small amounts of levonorgestrel released from the LNG-IUS enter the bloodstream and exerts systemic effects [6]. There are marked interindividual differences in the plasma levels achieved [6,7]. Levonorgestrel plasma concentrations in all LNG-IUS users are, however, small in comparison with levels in users of the progestin-only pill. The frequency of systemic side effects with different types of LNG-IUS has been reported in a number of studies [8–12]. Most of these studies have included mood changes and depression. Andersson et al. [8] reported a very low depression-associated removal rate of 0.5% in 1821 women using the LNG-IUS 20 μg/d over a 5-year period. A comparative study comprising 1124 women using the LNG-IUS 20 μg/d found mood changes or depression in 0.2% of users [10]. In a 2012 study comparing the LNG-IUS 20 μg/d and the even lower dose LNG-IUS 12 μg/d, 9.8% and 14% of users, respectively, reported mood alterations. Changes in mood should, however, be distinguished from major depressive disorder and in this study were not a reason for discontinuation [11]. Taken together the number of women experiencing serious depressed moods with the use of the LNG-IUS 20 μg/d and the LNG-IUS 12 μg/d seems to be very low. This might be different in women already suffering from anxiety or depressive disorder before initiating a progestin-only contraceptive. In such a situation caution is demanded. The frequency of these disorders has been reported to be increasing especially in very young women [13,14]. Better options might be a combined oral contraceptive or a copper-releasing intrauterine device (IUD). Studies of mood alterations in users of combined hormonal contraceptives have produced contradictory results, ranging from improvement to worsening only during the intermenstrual phase to different effects depending on the compound [15–17]. If a progestin-only method is initiated in a predisposed woman, the potential effects on mood should be addressed during counselling, and short-term follow-up is needed. Fortunately, we know from clinical experience that stopping the contraceptive method (LNG-IUS, progestin-only pill or implant) usually leads within days to recovery. A recent systematic review investigated the safety of hormonal contraceptives, including the LNG-IUS 20 μg/d, in women suffering from depression and bipolar disorder [18]. Limited evidence from six studies concluded that the use of the LNG-IUS and depot medroxyprogesterone acetate (DMPA) was not associated with worse clinical outcomes, while COCs tended to have a positive effect on mood. Furthermore, no negative impact on postpartum depression was found in DMPA users [19]. A large population-based study collected data on symptoms of depression over a period of 3 years among DMPA users [20]. Although it found an increased likelihood of reporting depressive symptoms, these symptoms subsided, relative to non-users, several months after DMPA discontinuation.

The report of Aleknaviciute et al. [1] has reignited the discussion by finding an increased cortisol response among LNG-IUS users in an adrenocorticotropic hormone stimulation test, as well as an elevated hair cortisol concentration.

It is important to research possible interactions between synthetic progestogens and the hypothalamic–pituitary–adrenal (HPA) axis. The authors demonstrated increased stress reactivity measured by cortisol response and heart rate pattern that differed significantly between naturally cycling women and users of the LNG-IUS 20 μg/d, the combined pill and the copper-releasing IUD. The study, however, has some limitations and prompts an open question:

- Investigating only one blood sample during the luteal phase of the natural cycle might not represent cortisol levels over the whole cycle. The cortisol level might be much higher during the estrogen-dominated follicular phase.
- The LNG-IUS 20 μg/d group included women with regular cycles and women with amenorrhoea. In women with regular cycles, the systemic action of levonorgestrel may be assumed to be less. Differences between the two groups should be analysed.
- There is no background information on the indication for the LNG-IUS 20 μg/d. Women using the LNG-IUS 20 μg/d because of heavy menstrual bleeding may have a different basic endocrine HPA profile, producing non-comparable groups with respect to the research question.
- Taking into account the research hypothesis (psychoendocrine mechanisms contributing to depressive symptoms with the LNG-IUS 20 μg/d), it is unclear why the authors did not test for affective symptoms during the study.
- The authors claimed that LNG-IUS users had chronically increased cortisol levels as determined by hair analysis. In the Trier Stress Test, however, the basic level of cortisol was the same in all groups.
- Are the findings, therefore, statistically significant but clinically non-significant? In other words, does the increase in the response tested indicate a pathological situation or is it in the normal range of responses?
- If the tested hypothesis was a levonorgestrel-induced activation of the HPA axis, why did the authors not include a study group taking the levonorgestrel-only pill, which has a much higher drug concentration? Findings among this group would have been more interesting than among a copper-releasing IUD group.

This is clearly an important study in an under-researched area concerning the interaction between contraceptive progestins and the HPA axis. Its findings cannot, however, at present be considered proof that the LNG-IUS is a major causative factor in the development of depressive symptoms among healthy women in general. Furthermore, several double-blind, placebo-controlled studies of glucocorticoid administration have found no effects on mood, emotional arousal or anxiety levels [21].

Summary

There is no doubt that the LNG-IUS leads to an increased but low serum level of levonorgestrel that can and does exert systemic effects. Studies demonstrate that very few women complain of severe mood alterations as a consequence of using an LNG-IUS. In women who have already experienced major depression, the LNG-IUS and other progestin-only contraceptive methods are not the first choice. If such a method is started, close clinical follow-up is necessary. It is unlikely that slightly higher cortisol levels in LNG-IUS users, as found in only one study, are associated with evidence of an increased risk of an adverse event that has not already been evaluated in considerably larger and more clinically appropriate studies. Taking a psychiatric history during counselling would help identify women who are more vulnerable to negative moods in association with hormone use.

For many years, the ESC has recommended the following steps for balanced and individualised counselling:

- Take a thorough medical history, considering especially any conditions that could cause a complication with use of a contraceptive method.
- Identify women predisposed to depressed mood by taking a past and current psychiatric history; ask specifically about ever-use of antidepressants.
- Include a family history to identify women at increased cardiovascular risk.
- Take time to cover in a personal history the woman's life situation, partnership and sexual life.
- After starting a new method offer a follow-up visit to discuss options in situations of severe or troublesome adverse events. Adverse events should include affective symptoms and sexual function.

Disclosure statement

G.S. Merki-Feld has received honoraria for lectures and/or participation in advisory boards from Bayer AG, MSD, Teva and Exeltis.

D. Apter's institution has received grants from Bayer, Estetra/Mithra, Exeltis, GSK and Merck/MSD during the last 5 years to conduct clinical trials. He has also taken part in advisory boards and has been an invited speaker at scientific meetings for Bayer, Estetra/Mithra, Exeltis, GSK and Merck/MSD on an *ad hoc* basis.

S. Raine contributed to advisory boards and did consultation work for MSD, Pfizer, Actavis/Allergan, Gedeon Richter and Bayer.

L. Shulman is a consultant for Bayer, Merck, Allergan and Teva.

J. Bitzer received honoraria for lectures and participation in advisory boards from Bayer AG, Merck, Libbs, Actavis, Teva, Exeltis, Gedeon Richter, Boehringer-Ingelheim, Vifor, Lilly, Pfizer, HRA, Abbott, Mithra, Pierre Fabre and Aspen.

G. Bartfai, G. Grandi, K. Haldre, M. Lech, R. Lertxundi, P. Lobo Abascal, F. Roumen, D. Serfaty and S. Skouby report no conflicts of interest.

References

[1] Aleknaviciute J, Tulen JHM, De Rijke YB, et al. The levonorgestrel-releasing intrauterine device potentiates stress reactivity. Psychoneuroendocrinology. 2017;80:39–45.

[2] Bitzer J. Hormonal contraception and depression: another Pill scandal? Eur J Contracept Reprod Health Care. 2017;22:1–2.

[3] Lanza di Scalea T, Pearlstein T. Premenstrual dysphoric disorder. Psychiatr Clin North Am. 2017;40:201–216.

[4] Yonkers KA, Brown C, Pearlstein TB, et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol. 2005;106:492–501.

[5] Paterson H, Clifton J, Miller D, et al. Hair loss with use of the levonorgestrel intrauterine device. Contraception. 2007;76:306–309.

[6] Nilsson CG, Lahteenmaki PL, Luukkainen T. Ovarian function in amenorrheic and menstruating users of a levonorgestrel-releasing intrauterine device. Fertil Steril. 1984;41:52–55.

[7] Luukkainen T, Lahteenmaki P, Toivonen J. Levonorgestrel-releasing intrauterine device. Ann Med. 1990;22:85–90.

[8] Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. Contraception. 1994;49:56–72.

[9] Luukkainen T, Allonen H, Haukkamaa M, et al. Five years' experience with levonorgestrel-releasing IUDs. Contraception. 1986;33:139–148.

[10] Sivin I, el Mahgoub S, McCarthy T, et al. Long-term contraception with the levonorgestrel 20 mcg/day (LNg 20) and the copper T 380Ag intrauterine devices: a five-year randomized study. Contraception. 1990;42:361–378.

[11] Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril. 2012;97:616–622. e1-3.

[12] Gemzell-Danielsson K, Apter D, Dermout S, et al. Evaluation of a new, low-dose levonorgestrel intrauterine contraceptive system over 5 years of use. Eur J Obstet Gynecol Reprod Biol. 2017;210:22–28.

[13] Skovlund CW, Kessing LV, Mørch LS, et al. Increase in depression diagnoses and prescribed antidepressants among young girls. A national cohort study 2000–2013. Nord J Psychiatry 2017;71:378–385.

[14] Brijnath B, Xia T, Turner L, et al. Trends in GP prescribing of psychotropic medications among young patients aged 16–24 years: a case study analysis. BMC Psychiatry. 2017;17:214.

[15] Lindberg M, Foldemo A, Josefsson A, et al. Differences in prescription rates and odds ratios of antidepressant drugs in relation to individual hormonal contraceptives: a nationwide population-based study with age-specific analyses. Eur J Contracept Reprod Health Care. 2012;17:106–118.

[16] Keyes KM, Cheslack-Postava K, Westhoff C, et al. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. Am J Epidemiol. 2013;178:1378–1388.

[17] Lundin C, Danielsson KG, Bixo M, et al. 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. 2017;76:135–143.

[18] Pagano HP, Zapata LB, Berry-Bibee EN, et al. Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: a systematic review. Contraception. 2016;94:641–649.

[19] Tsai R, Schaffir J. Effect of depot medroxyprogesterone acetate on postpartum depression. Contraception. 2010;82:174–177.

[20] Civic D, Scholes D, Ichikawa L, et al. Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. Contraception. 2000;61:385–390.

[21] Wirth MM, Scherer SM, Hoks RM, et al. The effect of cortisol on emotional responses depends on order of cortisol and placebo administration in a within-subject design. Psychoneuroendocrinology. 2011;36:945–954.