Contraceptives and Mood

5

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5.1 Background

The interest in how, and if, hormonal contraceptives influence mood has increased over the past years. This increase is potentially driven by an overall increased prevalence of mood and anxiety disorders in Westernized societies [1, 2], but potentially also because female hormonal contraceptive users are making themselves heard, as mood problems are less stigmatized nowadays than they used to be. Further, contraceptives are most frequently used, and most greatly needed, during a period of life when the first onset of a depressive episode or anxiety disorder may occur [3–5]. Because of the increasing interest and media coverage [6], many women, rightfully so, have questions regarding potential adverse mood effects from hormonal contraceptive use.

The clinical relevance of hormonal contraceptive-induced mood symptoms is also becoming more obvious. Mood symptoms, such as depressive symptoms, irritability, anxiety, and mood swings, are nowadays one of the major reasons for discontinuing hormonal contraceptive use [7]. Moreover, women who discontinue hormonal contraceptives often turn to less effective methods, thus increasing the probability of unintended pregnancies [8–10].

Three systematic reviews have been published over the past years, two dedicated to the mood effects of combined hormonal contraceptives and one to the progestogen-only contraceptives [11–13]. Altogether, these reviews covered the few placebo-controlled randomized trials, observational and cross-sectional studies that had been published up until 2016 and 2017, respectively. Besides pointing to the lack of high-quality evidence, the overall conclusion from these reviews was that the great majority of hormonal contraceptive users, including those using combined methods as well as progesterone-only methods, should not expect to experience negative

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mood [12, 13]. However, a smaller percentage of hormonal contraceptive users are at risk of experiencing a worsening of their mood. The mood effects appear relatively subtle and may be hidden in large observational studies, or even in the randomized controlled trials, as the proportion of women who are unaffected or even experience improved mood outnumber those who experience the negative effects [12]. The exact estimate of women who may experience mood symptoms while on hormonal contraception is essentially unknown, but proportions in the range of 4–10% have been suggested [11].

The lack of high-quality evidence as regards the influence of hormonal contraceptives on mood is still a major problem, and contradictory findings are imminent. Since these two reviews were published, two placebo-controlled randomized trials have been published [14, 15] and, in addition, three large-scale prospective cohort studies on the effect on mood in relation to hormonal contraceptives [16–18]. This review will discuss the high-quality evidence that is at hand, but also discuss the shortcomings and caveats that need to be taken into account when interpreting observational studies in the field.

5.2 Placebo-Controlled Randomized Trials

Randomized, placebo-controlled studies represent the highest level of evidence, and this is also true in the contraceptive field. However, the randomized trials are underpowered to detect more rare outcomes such as mental health problems requiring treatment.

The two recent placebo-controlled studies were investigator-initiated, meaning that they had received no funding from the pharmaceutical industry. The first study was a multicenter, randomized, double-blinded, placebo-controlled study including 202 healthy women. The women were randomized to a combined pill containing 1.5 mg estradiol and 2.5 mg nomegestrol acetate or placebo for three treatment cycles [14]. The main outcome measure was the Daily Record of Severity of Problems (DRSP), which was filled out daily during one baseline cycle and during the final treatment cycle. Secondary outcomes included the Montgomery-Åsberg Depression Rating Scale, filled out at baseline and during the third, and final, treatment cycle. The use of daily ratings on the DRSP opened up for the possibility to investigate mood changes across the treatment cycle, covering the menstrual, premenstrual, and intermenstrual phases. Use of the combined pill was associated with small, but statistically significant, increases in mean anxiety (0.22; 95% CI 0.07–0.37), irritability (0.23; 95% CI 0.07–0.38), and mood swings scores (0.15; 95% CI 0.00–0.31) during the intermenstrual phase but not in the other treatment phases. Further, a significant premenstrual improvement in depression was noted (−0.33; 95% CI 0.62–0.05). While the study was not powered to detect differences in women who had a clinically relevant change in mood, the proportion of women who reported a clinically relevant mood deterioration was 24.1% among those allocated to COC and 17.0% among the placebo users. In addition, the number of women with new-onset subclinical depression during treatment did not differ

between the oral contraceptive group and the placebo group, 9.6% in the combined hormonal contraceptive users and 6.4% in the placebo group [14].

The second placebo-controlled randomized trial included 340 women randomized to a combined pill containing 30 μg ethinylestradiol and 150 μg levonorgestrel [15]. Primary outcomes in this trial were general well-being, assessed by the Psychological General Well-Being Index (PGWBI), and depressed mood, captured by the Beck Depression Inventory (BDI). Treatment with the combined hormonal contraceptive led to significantly reduced general well-being compared with placebo, with the dimensions contributing to the overall result being reduced positive well-being, reduced self-control, and reduced vitality. No difference in depressed mood was noted between the combined pill and placebo, and the proportion of women with moderate to severe depressive symptoms at the end of the trial was similar (7% in both groups) [15].

These relatively modest findings of these two recent placebo-controlled trials are in line with Graham and colleagues who conducted a placebo-controlled, double-blind comparison of a COC (EE 30 μg/0.15 mg levonorgestrel) and a progestogen-only contraceptive pill (levonorgestrel 0.03 mg) [19]. The study included 150 women and was carried out in two contrasting cultures. Besides differences at baseline in mood between the two settings, there were no differences between the placebo and the COC in terms of daily ratings of depression or irritability. However, the COC was associated with more negative mood changes than the POP, but with very small effect sizes [19]. Yet another placebo-controlled trial reported on inner city adolescents ($n = 76$), who were randomized to 20 μg EE/0.10 mg levonorgestrel or placebo for treatment of dysmenorrhea. Depressed mood was a secondary outcome of the trial and was assessed by use of the Center for Epidemiologic Studies Depression Scale (CES-D). The adolescents had relatively high depression scores already at baseline, but throughout the study, depression scores decreased equally in the treatment and placebo groups [20]. No information on frequency of women who deteriorated or improved was given in these two trials.

A number of conclusions can be drawn from these randomized trials, which thus far represent the highest level of evidence on hormonal contraceptive-induced mood changes. First, the overall effect sizes for the mood effects that were noted were small. This finding clearly points to the complexity of studying how hormonal contraception affect women's mood, where some women will report improved mood, the great majority unchanged mood, and a smaller fraction of women clearly being negatively affected by the combined hormonal contraceptive. An example of this distribution is given in Fig. 5.1, derived from one of the placebo-controlled trials.

Secondly, none of these two trials was able to detect a worsening in depressive symptoms or an increase in the proportion of women with clinical relevant depressive symptoms at the end of the trial. In fact, one of the trials reported on improved depressive symptoms during the premenstrual phase of the treatment cycle, in line with evidence suggesting that hormonal contraceptives can be used to treat premenstrual dysphoric disorder [21, 22]. Further, mood worsening and depressive symptoms were also relatively common among the placebo users, emphasizing that women are at increased risk of depressive symptoms, depression, and anxiety

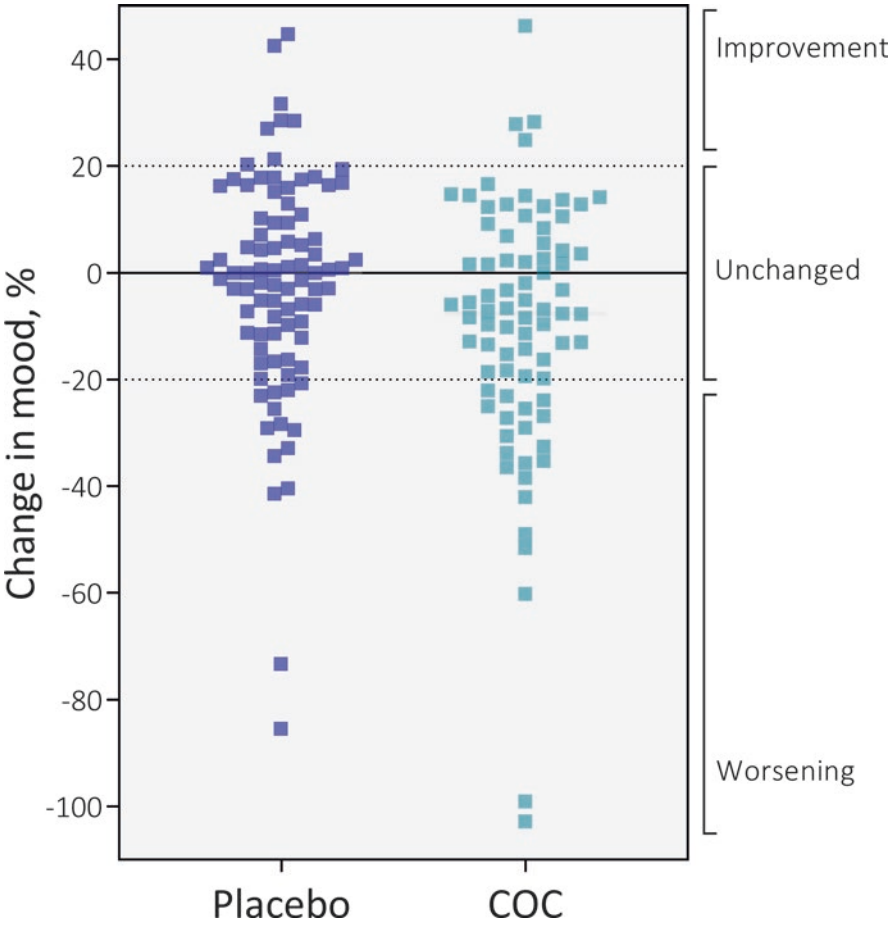

Fig. 5.1 Change from baseline to the final treatment cycle in summed mood scores on the Daily Record of Severity of Problems scale. The summed mood score consisted of anxiety, mood swings, irritability, and decreased interest in usual activities

disorders, just because they are women [23], and especially during this time period in their lives [3–5]. Healthcare providers should be aware that mental health problems are common in women and that they not always (or rarely, see below) are causally related to the use of hormonal contraceptives.

However, at the same time, both studies clearly demonstrated that the combined pill is associated with minor mood changes in symptoms like increased irritability, increased anxiety and mood swings, and lowered general well-being. For some women, these modest changes in mood may be clinically relevant and the final push to a mental health problem in need of psychotropic treatment. Overall, modern contraceptive counselling should include a discussion about the potential risk of minor mood disturbances while on treatment.

5.3 Observational Studies

While none of these studies was able to address anything but subtle changes in affective symptoms, most often outside the clinical range, they cannot be used to estimate relatively rare outcomes of hormonal contraceptive use, like major depressive disorder. For such outcomes, large-scale observational studies are needed. Indeed, in 2016 Skovlund and collaborators published a large-scale prospective cohort study on the risk of developing depression in relation to hormonal contraceptive use [17]. The study was unique in the sense that it was the first longitudinal study in the field. The longitudinal design, in turn, has the advantage of avoiding the healthy user bias. The healthy user bias, or survivor bias, implies that women who develop mood problems while on hormonal contraception are much more inclined to discontinue, leaving a core of healthy, unaffected users. The healthy user bias is a common explanation why most cross-sectional studies report that hormonal contraception is associated with lower risks of depression and other psychiatric problems than non-use [12, 13, 24]. The study by Skovlund and colleagues used depression diagnoses, captured in specialized psychiatric care, and filled prescription for antidepressant drugs as outcomes, ultimately not only capturing major depression but also a range of anxiety disorders for which antidepressant drugs are also used. In essence, the authors found an increased relative risk of antidepressant treatment in oral combined contraceptive users of 1.2 (95% CI 1.22–1.25) and progestogen-only contraceptive users of 1.3 (95% CI 1.27–1.40), compared with non-users, which would translate to an absolute risk of antidepressant use of 0.9/100 hormonal contraceptive users [25]. The risk was most pronounced in adolescents, where the overall risk of filling an antidepressant prescription was 1.8 (95% CI 1.75–1.84) in oral combined users and 2.2 (95% CI 1.99–2.52) in progestogen-only contraceptive users. After the age of 25, the association between hormonal contraceptive use and antidepressant treatment was no longer evident, according to the authors, due to the healthy user bias [17]. The study received massive media coverage but has also met with criticism from the scientific community [6]. While impressive in numbers and design, the study has its own set of important biases, which were not adequately addressed, the most important being confounding by indication. Confounding by indication means that the very reason some women are using hormonal contraception could, in itself, be a risk factor for depressive or anxiety disorders. Besides contraception, many women use hormonal contraceptives for medical reasons, such as dysmenorrhea, endometriosis, polycystic ovary syndrome, acne, premenstrual syndrome, premenstrual dysphoric disorder, or heavy menstrual bleeding. Indeed, each of these conditions has been associated with reduced quality of life, depressed mood, anxiety symptoms, or depressive and anxiety disorders [26–34]. While the study by Skovlund adjusted for PCOS and endometriosis, common complaints in adolescents often include dysmenorrhea and acne. Confounding by indication may also be much more subtle than what is captured with these diagnoses, and there is some evidence in the study by Skovlund and colleagues that such mechanisms may have influenced the results. In comparison with levonorgestrel-containing pills, the risk of antidepressant treatment was higher in users of

cyproterone acetate-containing combined contraceptives, in users of pills containing natural estrogen and in patch or vaginal ring users. Some of these products have been linked to treatment of acne and heavy menstrual bleeding, whereas the vaginal ring and the patch may be prescribed more often to women who have problems with adherence to the daily pill intake. The latter indication is difficult to capture in any register and may mean many things. Indeed, women who use COC for reasons other than contraception are more likely than non-users to report depressive symptoms (OR 1.32, 95% CI 1.07–1.62).

Ultimately, there is no biological reason why the vaginal ring or the patch should confer an increased risk in relation to a levonorgestrel-containing pill, given the relatively similar, or even lower, serum concentrations of the steroid hormones [35, 36]. Further, these findings are at odds with randomized controlled trials comparing the ring or patch with oral contraceptives, showing either positive effects of the transdermal route or no difference between the regimens in depressive symptoms or well-being [37, 38].

Other researchers have also pointed to the absence of dose-response relationships as concerns the progestogen-only preparations, where the low-dose hormonal intrauterine device (IUD) was associated with somewhat higher risks than the systemic oral preparations [13]. Without biologically plausible explanations, the estimates from the observational studies must be questioned.

Similar findings were reported by a Swedish cohort study, investigating the association between hormonal contraceptives and psychotropic drug use (defined as filled prescription of antidepressants, benzodiazepines, atypical benzodiazepines, antihistamine anxiolytics, and melatonin), with a 1-year follow-up. The risk of psychotropic drug use was particularly noticeable in hormonal contraceptive users 12–14 years of age (or for combined oral pills 3.3 (95% CI 2.85–3.81)), followed by women 15–17 years of age (or for combined oral pills 1.52 (95% CI 1.41–1.64)). Already by age 18–20 years were the estimates minor (or combined oral pills 1.08 (95% CI 1.01–1.16)), and after the age of 20, the increased risk disappeared (or combined oral pills 0.94 (95% CI 0.89–1.00)). While the risk reduction in the adult women most likely is due to the healthy survivor bias, it may equally well be argued that most women who receive hormonal contraception in Sweden between the ages of 12 and 14 do so because of medical reasons, such as dysmenorrhea [39]. Further, these medical indications may not be captured in any of the registers (i.e., not being accessible for statistical adjustment), as diagnoses are established by physicians. In Sweden, the grand majority of contraceptive prescribers are midwives, and while they will not formally record any diagnoses, they will most likely respond to the menstrual problems young girls present with. The study by Zettermark and colleagues also found that non-oral hormonal contraceptives, i.e., the ring, the patch, and the implant, generally carried an increased risk in comparison with the oral preparations, regardless whether being combined or progestogen-only non-oral contraceptives. As an explanation to this finding, the authors themselves argued that women in need of methods that require less adherence may represent a more vulnerable group of women, thus suggesting some confounding by indication. Overall, the use of psychotropic medication was low in the population, with 3.7% of hormonal

contraceptives users filling a prescription for any of these drugs during the follow-up, while the corresponding number in the non-users was 2.5%, meaning that the absolute risks are low. These findings are in stark contrast with observational studies in teenagers, reporting no worsening of depressive symptoms or health-related quality of life upon initiation of hormonal contraceptives [40, 41].

Yet another large-scale study of mood effects from hormonal IUD was published recently, although again, the evidence must be regarded with caution. Using the UK general practice electronic medical records, the researchers demonstrated that use of the levonorgestrel IUD, as compared to copper IUDs, was associated with increased reporting of depression (assessed as filled prescription of antidepressants, HR 1.17, 95% CI 1.08–1.26), anxiety (HR 1.18, 95% CI 1.08–1.29), and sleep problems (HR 1.22, 95% CI 1.08–1.38) [18], whereas panic attacks and restlessness were unaffected. These effects were only evident in women with no previous psychiatric history, whereas women with such histories did not report increased mood problems with the hormonal IUD. At the same time, the authors acknowledged substantive differences in the baseline characteristics of the women who choose (or were advised) a hormonal or a copper IUD, making robust conclusions difficult.

Ultimately, the findings from these observational studies point to a small, albeit, increased risk of depression, or other mental problems from hormonal contraceptive use. The absolute risks for hormonal contraceptive-induced mental health problems, where antidepressant treatment is needed, are small and will not affect the great majority of hormonal contraceptive users. Importantly, confounding by indication is likely present in the observational studies, meaning that the estimates may be exaggerated, further reassuring the women in need of hormonal contraception.

5.4 What Women Are at Risk for Negative Effects of Hormonal Contraception?

Given the small, albeit significant, increased risk of hormonal contraceptive-induced mood symptoms, some mentioning of risk factors is warranted. Young age, psychiatric history, genetics, personality traits, interpersonal relationships, and socioeconomic factors are likely to contribute to the adverse mood symptoms experienced by some of the hormonal contraceptive users [16, 42–44], but overall, relatively little high-quality research has been conducted in this area.

The most obvious risk factor is if women claim they have prior experience of hormonal contraceptive-induced mood problems. In a small, randomized placebo-controlled trial, Gingnell and colleagues included 34 women with previous negative mood experience from hormonal contraceptives and randomized them to a levonorgestrel-containing pill or placebo for one treatment cycle [45]. When re-exposed to the combined hormonal contraceptive, the women experienced depressive mood and mood swings. However, only one third of these susceptible women experienced a clear-cut mood worsening during re-exposure. The findings suggest that self-reported contraceptive-induced mental health problems should be taken into account when counselling women. However, these reports do not infer a causal

relationship with the contraceptive, i.e., the mental health problems could have been caused by life stress or other reasons. If interested, women should not be discouraged to try hormonal contraceptives again.

Previous psychiatric history seems to play a role, although findings are not unanimous [12]. Two prospective trials found that depressed mood was associated with hormonal contraceptive-induced moodiness [46, 47], whereas two other prospective studies indicated that women with high levels of depressive symptoms at baseline were those most likely to benefit from the hormonal contraceptive [48, 49]. However, a sub-analysis of a randomized placebo-controlled trial indicated that much of the adverse mood effects noted in the trial were, in fact, driven by women with previous or ongoing mood or anxiety disorders [50].

5.5 Mood Symptoms Are Likely Caused by the Progestogen

It seems reasonable to assume that it is the progestogen of the hormonal contraceptive that causes the mood problems. Several lines of evidence substantiate this assumption. First, one of the randomized placebo-controlled trials indicated that mood worsening was only present in the intermenstrual phase, not in the premenstrual phase [14]. Thus, when the placebo users were exposed to high endogenous levels of progesterone during the luteal phase, no difference to the hormonal contraceptive users could be detected [14]. Secondly, the risk of mental health problems in observational studies was present in the progestogen-only users as well as in the combined hormonal contraceptive users [16, 42]. In addition, a long line of evidence suggests that progesterone has multiple negative effects on emotion processing [51], emotional circuits in the brain, including the amygdala [52], and on mood symptoms in women across the life span [53]. Further, the type of progestogen may play a role for the surfacing of symptoms during combined hormonal contraceptive use. A few direct head-to-head comparisons of mood effects have been conducted, and anti-androgenic progestogens seem to be more advantageous in this respect. Using a single-blind design, Kelly and colleagues compared EE 30 μg/drospirenone with EE 30 μg/levonorgestrel in 280 healthy females during seven treatment cycles. Using the Menstrual Distress Questionnaire (MDQ) as outcome, a greater reduction in negative affect was noted during the menstrual phase among women using the drospirenone-containing pill [54]. Sangthawan and colleagues performed an open-label, but randomized, study comparing EE 30 μg/drospirenone with EE 30 μg/levonorgestrel in 99 women. At completion, negative affect scores in the premenstrual phase were lower in women randomized to the drospirenone-containing pill. The difference in negative affect was mainly driven by changes in anxiety levels, irritability, and depressed mood [55].

Using the same outcome measure, Bruni and colleagues found no difference in overall emotional well-being between EE 30 μg/desogestrel and mono- or triphasic EE 30 μg/gestodene-containing pills among the 1721 women who completed the trial. However, for individual MDQ scores, the EE 30 μg/desogestrel compound was more favorable, for instance, “lack of control” [56]. Winkler and co-workers

compared EE 20 μg/desogestrel and EE 20 μg/levonorgestrel in 788 women. The overall mean Profile of Mood States (POMS) change from baseline was greater in the EE 20 μg/desogestrel than in the EE 20 μg/levonorgestrel group, suggesting a slightly greater improvement in quality of life in the former group [57].

5.6 Final Conclusions

At present there is sufficient evidence to conclude that hormonal contraceptives are associated with small changes in anxiety, irritability, and well-being. However, the proportion of women who develop these mood symptoms are out-numbered by the women who are unaffected or even improved, exemplified by the very small effect sizes noted in the placebo-controlled trials.

While the mean effect sizes are small, for some women the changes in mood may be clinically relevant or even represent the final push to a mental health problem in need of psychotropic treatment. Observational studies have provided some evidence that hormonal contraceptive use may lead to mental health problems in need of treatment. The absolute risk for this outcome is low, in the range of 1/100 hormonal contraceptive users. However, because of residual confounding in the observational studies, these estimates are likely overestimated.

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