Hormonal contraception and depression: another Pill scandal?

Publication of the article by Skovlund et al. ‘Association of hormonal contraception with depression’ [1] has produced a strong media reaction in several countries, with recent headlines like those in the German magazines *Gala* ‘Finally proven: the Pill causes depression’ and *Brigitte* ‘Danish scientists show the Pill increases the risk of depression in young women by 80%’. Although the article’s authors refer to association and not causality in the title and in the conclusion, and indicate that ‘further studies are warranted to examine depression as a potential adverse effect of hormonal contraception’, social and other media have seized on the study as proof that the Pill causes depression. After the media storms surrounding thromboembolic risk and sexual dysfunction, we now seem to have another public health issue linked to hormonal contraceptives. No doubt we will soon read about the money we could save if women stopped taking the Pill, by reducing the consumption of antidepressants.

First, we should ask the most important question: does this study prove that combined hormonal contraceptives cause depression? The answer, for several reasons, is no.

- Depression is a multifactorial disease in which genes, environment, life events, distress and hormones interact in a complicated, individual way. This study did not have the design or the information to control for these possible confounders.
- The diagnosis of depression is even more difficult than the diagnosis of thrombosis (itself quite difficult). The study took as an outcome not the diagnosis of depression but treatment with antidepressants, as a substitute for diagnosis. Another study outcome was hospitalisation due to depression. This is a methodological problem. It may well be that women who take the Pill have more connection with health care services and are more likely to report symptoms that lead to a prescription. It may well be that pre-existing depressive disorder is diagnosed at the time when the woman is using a combined oral contraceptive (COC) containing a specific progestogen (see below).
- The study’s ‘sensitivity analysis’ was insufficient to exclude psychosocial changes that might have contributed to the depressed mood of individual women.
- No information was given about the women who stopped taking COCs because of mood changes and what the outcome was. This is, however, what happens in real life and it is important to know whether the reported side effect disappeared after stopping or changing the contraceptive.
- In terms of absolute risk, the importance of the increase in risk seems much less impressive. Among women not taking hormonal birth control, 1.7% took antidepressants and 0.28% received a diagnosis of depression at a psychiatric hospital. By comparison, 2.2% of women who started birth control began taking antidepressants afterwards and 0.3% were diagnosed with depression at a hospital. Basically, about 0.5% of women who began
hormonal contraception developed depression who might not have developed it otherwise.

- There are several results that raise concerns about biological plausibility. Why should teenagers using the patch or the ring have a statistically higher risk of depression than those using oral preparations containing the same steroids? It is hard to believe that the small pharmacokinetic and pharmacodynamics differences would account for this difference.

Apart from these limitations the publication suffers lacked a more critical discussion of other studies that reached different or conflicting results. For instance, a study by Keyes et al.[2] indicated a protective effect of hormonal contraception with respect to affective disorders. A Swedish observational study published in this journal found a positive association between the use of progestogen-only contraception and antidepressants, particularly among teenagers.[3,4] Regarding combined hormonal contraception, teenage users were more likely, but older women less likely, to be prescribed antidepressants compared with non-users. Another study, not mentioned in the Skovlund et al. article, may contribute to understanding the complexity.[5] This study included women under the age of 40 years suffering from major depression: 223 used combined hormonal contraceptives, 58 used progestogen-only preparations and 948 did not use hormonal contraceptives. The women who used combined hormonal contraceptives were significantly less depressed than the women who did not. Users also showed higher physical fitness and less comorbidity with compulsive disorders.

The second question is: does this study show that low or depressed mood in some women may be related to the progestogenic component of hormonal contraception? The answer is a cautious yes. This is something we already know not only from clinical experience but also from studies on the impact of hormones on mood and affect.

There is a huge body of literature about the impact of steroid hormones on the most important neurotransmitters in the brain. The interaction is complicated and depends not only on the presence or level of hormones but also on the hormone receptors in the brain. The vulnerability of women to endogenous steroid hormones has been very well studied in research aimed at trying to understand the hormonal mechanisms involved in premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). These studies show that in vulnerable women the use of progestogens may increase the symptoms of depressed mood. There seems to be a difference between progestogens: antiandrogenic or neutral progestogens show a more favourable action compared with androgenic progestogens. The final action in the individual patient is, however, complicated by the fact that the estrogen component has a mood-elevating effect while at the same time reducing circulating levels of free testosterone, which may have a mood-lowering effect. We know from studies of the progestogen drospirenone that this COC is able to treat the psychiatric affective disorder PMDD apparently as effectively as the gold standard treatment with selective serotonin reuptake inhibitors.[6]

Other studies have shown the complexity and sometimes contradictory action of synthetic steroids on the brain: Oinonen and Mazmanian[7] found that, compared with non-users, oral contraceptive (OC) users experienced less variability in affect across the entire menstrual cycle, and less negative affect during menstruation (i.e., during withdrawal bleeding).
In women with negative mood and affect change related to OC use, potential mediators of the relationship between OCs and mood or affect have been identified: a history of depression, psychiatric symptoms, dysmenorrhea and premenstrual mood symptoms prior to OC use; a history of pregnancy-related mood symptoms; a family history of OC-related mood complaints; being in the post-partum period; and age. Furthermore, a lower ratio of progestogen to estrogen is associated with more negative mood changes in women with a history of premenstrual mood symptoms; a higher progestogen to estrogen ratio is associated with increased negative mood effects in women without such a history; monophasic OCs have a greater stabilising effect on mood compared with triphasic OCs.

In an important study, Rapkin et al. [8] showed that in healthy women without underlying mood or anxiety disorder the use of a low-dose OC did not result in adverse psychological symptoms despite a significant reduction in neuroactive steroids, indicating that individual vulnerability to steroid action in the brain, as we know from PMS and PMDD, is a precondition for adverse effects and that in healthy women fluctuations of neurosteroids are well tolerated.

In summary, we do see women who react with depressed mood when taking certain hormonal contraceptives (probably related to the particular effect of the specific progestogen on receptors in the limbic system). Interestingly enough, the same women may feel better by changing progestogen. The Danish study [1] thus confirms what the European Society of Contraception and Reproductive Health have always advocated: that contraceptive counselling and care should be tailored to the individual.

- Carry out a biopsychosocial assessment of the woman, including her mental condition and environmental distress, as part of her psychosocial and cultural profile.
- Provide a choice of contraceptive methods, including the use of different progestogens with differential actions on different parts of the body such as the reproductive system, the cardiovascular system, the skin and hair, and last but not the least the brain.
- During use, ask proactively about side effects, including questions about sexual function and affective symptoms, and explore factors contributing to any complaints that may be due to the contraceptive used or to other causes.
- Discuss changing the contraceptive method or changing the type of hormonal contraceptive. Ask not only about bleeding or physical symptoms but also about mood and sexuality.

References


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激素避孕和抑郁：另一个避孕药片的流言？

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Skovlund 等作者发表的文章“激素避孕与抑郁症的关系” [1]在几个国家产生了强烈的媒体反应，最近的头条例如德国杂志 Gala“最后证明：药物引起抑郁症”和 Brigitte “丹麦科学家证实药片增加 80％年轻女性患抑郁症风险” 虽然文章的作者在标题和结论中提到是关系而不是因果关系，并指出“确定抑郁症是否作为激素避孕的潜在不利影响需要进一步的研究”，社会和其他媒体抓住了药物引起抑郁症的研究作为证据。在媒体风暴围绕血栓栓塞性风险和性功能障碍后，我们现在似乎有了与激素避孕药有关的另一个公共卫生问题。毫无疑问，我们将很快读到如果妇女停止服用避孕药，通过减少抗抑郁药的消费，我们可以节省钱。
首先，我们应该问最重要的问题：这项研究证明复方激素避孕药导致抑郁症吗？由于几个原因，答案是否。

- 抑郁症是一种多因素疾病，其中基因、环境、生活事件、痛苦和激素以复杂的方式相互作用。这项研究没有设计或没有信息来控制这些可能的混杂因素。
- 抑郁症的诊断比血栓形成的诊断更困难（本身相当困难）。该研究作为结果不是抑郁症的诊断，而是用抗抑郁药治疗，作为诊断的替代。另一项研究结果是由于抑郁症的住院治疗。这是一个方法问题。很可能，服用药物的妇女与保健服务有更多的联系，更有可能报告开处方的症状。可能是当女性使用含有特定孕激素的复方口服避孕药（COC）时，预先存在的抑郁症被诊断出来（见下文）。
- 没有提供关于由于情绪变化而停止服用COC的女性的信息以及停药之后的结果。然而，这在现实生活中是发生的，重要的是要知道所报告的副作用是否在停药或改变避孕药后消失。
- 在绝对风险方面，风险增加的重要性似乎不那么令人印象深刻。在不服用激素避孕的妇女中，1.7%的患者服用抗抑郁药，0.28%的患者在精神病医院接受抑郁症诊断。相比之下，2.2%的开始避孕的妇女开始服用抗抑郁药，0.3%的妇女在医院被诊断为抑郁症。基本上，约0.5%的开始用激素避孕的女性发展成抑郁症，否则可能不会发展。
- 有几个结果引起了对生物学然性的关注。为什么使用补丁或戒指的青少年比使用含有相同类固醇的口服制剂的青少年有更高的抑郁风险？很难相信小的药代动力学和药效动力学差异解释这种差异。

除了这些限制，该出版物缺乏对其他研究达到的不同或冲突结果的更批判的讨论。例如，Keyes等人的研究[2]表明激素避孕对情感障碍的保护作用。在这份杂志上发表的一项瑞典观察性研究发现，使用单纯孕激素避孕和抗抑郁药存在相关，特别是青少年之间[3,4]。关于复方激素避孕，与非使用者相比，青少年使用者更可能被给予处方抗抑郁药，但老年妇女不太可能。Skovlund等人的文章中没有提到的另一项研究可能有助于理解复杂性[5]。这项研究包括40岁以下患有重度抑郁症的妇女：223名使用复方激素避孕药，58名使用孕激素制剂，948名未使用激素避孕药。使用复方激素避孕药的妇女的压力显著低于没有用药的妇女。用药的女性还表现出更高的身体健康和与较少的强迫性疾病的合并症。

第二个问题是：这项研究是否表明一些女性的低或抑郁情绪可能与激素避孕的孕激素组分有关？答案是谨慎的，肯定的，这是我们不仅从临床经验，而且从激素对情绪和情感的影响的研究中已经知道的东西。
关于类固醇激素对大脑中最重要的神经递质的影响有大量的文献。相互作用是复杂的，并且不仅取决于激素的存在或水平，而且取决于脑中的激素受体。妇女对内源性类固醇激素的脆弱性在研究中已经被非常好地研究，目的在于试图理解涉及经前综合征（PMS）和经前焦虑障碍（PMDD）的激素机制。这些研究表明，在弱势妇女使用孕激素可能会增加抑郁情绪的症状。孕激素似乎存在差异：与雄激素孕激素相比，抗雄激素或中性孕激素显示出更有利的作用。然而，个体患者中的最终作用因以下事实而复杂化：雌激素组分具有升高心情的作用，同时降低游离睾酮的循环水平，其可具有降低心情的作用。我们从孕激素屈螺酮的研究中知道，这种COC能够治疗精神性情感障碍PMDD，显然与用选择性5-羟色胺再摄取抑制剂的金标准治疗一样有效[6]。

其他研究表明合成类固醇对大脑的复杂性和有时相互矛盾的作用：Oinonen和Mazmanian[7]发现，与非使用者相比，口服避孕药（OC）者在整个月经周期中的影响变异性较小，在月经期间（即，在中断出血期间）具有较少的负面影响。

在有与OC使用相关的负面情绪和情感变化的妇女中，已经鉴定出OC与情绪或情感之间的关系的潜在调解者：在使用OC之前的抑郁症、精神病症状、痛经和经前情绪症状的历史；怀孕相关情绪症状的病史；OC相关情绪主诉的家族史；在孕期和年龄。此外，孕激素与雌激素的较低比率与具有月经前情绪症状的妇女中更负面的情绪变化相关；更高的孕激素与雌激素的比例与没有这种病史的妇女的负面情绪效应增加相关；单相OC与三相OC相比对情绪具有更大的稳定作用。

在一项重要研究中，Rapkin等人[8]表明，尽管神经营活性类固醇显著减少，在没有潜在情绪或焦虑障碍的健康女性中，使用低剂量的OC不会导致不良的心理症状，表明个体对脑中类固醇作用的易感性，从PMS和PMDD知道，这是不利影响的前提条件，在健康的女性神经类固醇的波动是良好的耐受。

总之，我们确实看到，当妇女服用某些激素避孕药（可能与特定孕激素对边缘系统受体的特定作用有关）时抑制了情绪反应。有趣的是，相同的女性可能通过改变孕激素感觉更好。因此，丹麦研究[1]证实了欧洲避孕和生殖健康协会一贯主张的：避孕咨询和护理应该针对个人。

- 对妇女进行生理心理社会评估，包括她的精神状况和环境压力，作为她心理社会和文化背景的一部分。
- 提供避孕方法的选择，包括使用不同孕激素在身体不同部位的不同作用，如生殖系统、心血管系统、皮肤和头发，以及最后的大脑。
在使用过程中，主动询问副作用，包括有关性功能和情感症状的问题，并探讨造成任何可能由于使用避孕药或其他原因引起的主诉因素。

讨论改变避孕方法或改变激素避孕药的类型。不仅要问出血或身体症状，还要考虑情绪和性行为。

参考文献:


