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Case Report

Development and remission of depressive symptoms and treatment with hormonal contraceptives

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We present two cases of female patients with a history of depression who developed depressive symptoms after treatment with hormonal contraceptives (HC) in the form of combined oral contraceptive pill, progestin-only pill and combined contraceptive vaginal ring. The presented two cases are based on the women's medical records complemented by personal interviews. The existing literature on the effects of HC on depression is inconclusive. Patient-based decisions with consideration of the individual history and predispositions are recommended when starting oral contraceptives. If depressive symptoms occur, decisions regarding discontinuation need to be made on an individual basis.

INTRODUCTION

Hormonal contraceptives (HC) may contain either synthetic oestrogen and progestin in combination or progestin-only and act by inhibiting the secretion of luteinizing hormone and follicle-stimulating hormone, which, among other effects, also blocks ovulation. Depression is one of several commonly reported side-effects in the use of HC in women.

Severe unipolar depression is almost twice as frequent in females as in males after puberty with a lifetime prevalence rate in the Danish population of 15.8% for women compared with 8.6% for men [1]. This is not the case before puberty, when the frequency of depression is equally distributed between the sexes [2]. Besides, women are especially susceptible to depressive episodes during periods of fluctuation in sex hormones (e.g. pregnancy, the post-partum period and menopause) [3].

This case report describes the medical histories of two female patients with prior psychiatric history who developed depressive symptoms after initiating treatment with HC in the form of both combined contraceptive vaginal ring, combined oral contraceptive pill (COCP) and progestin-only pill (POP).

MEDICAL HISTORY

A 31-year-old woman, known with recurrent depression since her late teenage years, was referred to our psychiatric ambulatory care clinic, in Hilleroed, Denmark. She was being treated with citalopram 40 mg daily and quetiapine 25 mg nightly. Additionally, she used a combined contraceptive vaginal ring with etonogestrel and ethinylestradiol. Laboratory tests were normal. The Hamilton Depression Rating Scale (HAM-D_{17}) score was 24, corresponding to moderate depression. Treatment was switched to amitriptyline, which was titrated to 175 mg daily under ECG monitoring. Her HAM-D_{17} reduced to 17, corresponding to mild depression. The patient interrupted contraception with the vaginal ring and saw gradual improvement over the following weeks, until a sudden and acute worsening occurred, shortly after the patient re-initiated contraception with combined cyproterone acetate-ethinyl oestradiol pill (COCP). There was a concomitant fall in plasmatic concentration of amitriptyline and its metabolite nortriptyline from 327 to 279 mmol/l even though no major impact was expected from the interaction between amitriptyline and cyproterone acetate-ethinyl oestradiol. The daily dose of amitriptyline was increased to 200 mg without effect. HC was interrupted and amitriptyline daily dose was simultaneously decreased to 150 mg, with a subsequent improvement in depressive symptoms and an increase in plasmatic concentration of amitriptyline/nortriptyline to 308 mmol/l. One month later, another acute worsening was noted, almost simultaneously with the initiation of treatment with combined contraceptive vaginal ring with etonogestrel and ethinylestradiol. HC was again interrupted, with a

subsequent clear improvement in depressive symptoms. The patient remained stable without depression for the following 6 months.

A 33-year-old pregnant woman in Week 20 + 5 was referred to our psychiatric ambulatory care clinic because of a severe depression during a previous pregnancy, which was terminated by elective abortion at Week 10. Since her previous depressive episode, she had been in antidepressant treatment with citalopram 30 mg daily. She developed no depressive symptoms during this pregnancy. Three months after giving birth, she started treatment with HC in the form of POP (norethisterone) and shortly after developed depressive symptoms despite continued antidepressant treatment. She was advised to discontinue HC, and her depressive symptoms disappeared completely within a week. At 6-month follow-up, she was still without depression.

DISCUSSION

These two cases indicate an association between the use of HC and depressive symptoms.

Epidemiological studies of this association have generated conflicting results. A large Australian population study found no independent effect of oral contraceptive pill use on depressive symptoms in young women [4], whereas a Norwegian study found a protective effect of the combined contraceptive pill and a deleterious effect of progestin-only agents in regard to mood disorders [5]. It could, therefore, be expected that the mood-altering effect would be more severe with the POP. However, these two cases indicate a worsening effect on depressive symptoms for both POP and COCP.

Animal studies suggest that oestrogen is an important modulator of the serotonin system in the brain [6], which might explain the protective effect that oestrogen-based HC might have against depressive symptoms as reported by the Norwegian study [5]. Yet another study found a lower mean level of oestradiol in depressed women [7], which could be important for the understanding of the hypothalamic–pituitary–ovarian axis and the associations between depressive symptoms and HC.

It is also possible that the association is related specifically to the hormonal fluctuations that follow the initiation of HC treatment, as is the case with the association between mood disorders and natural fluctuations in sex hormones [3].

The two patients had a known history of depression, and the risk of relapse was, therefore, present in both patients. Moreover, previous depression is associated with a higher risk of depression during pregnancy and the first months after birth [8]. In the second patient, it is unknown whether COCP would pose a smaller risk of relapse than POP or whether a higher dose of antidepressant, might have prevented the episode, since 30 mg daily of citalopram could be considered insufficient [9].

Unlike orally administered HC, the vaginal ring avoids gastrointestinal absorption and hence first-pass metabolism. In fact, the vaginal ring has been reported to be associated with a smaller risk of depression and irritability than COCP [10]. In the first patient, however, both forms of administration were associated with depression relapse.

Given the uncertainty surrounding the associations between HC and depressive symptoms, the case histories presented here testify to the importance of due diligence and caution in the treatment with HC in female patients with a history of or predisposition for depression. Caution should be used when starting up treatment with HC in women diagnosed with depression, since it might in some cases lead to worsening of the depressive symptoms. Likewise, attention should be paid to the pre-existing use of HC in women who develop depression, as discontinuation of HC might in some cases be sufficient to treat the depression.

CONFLICT OF INTEREST

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