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ARTICLE

Hormonal contraception and mood disorders

SUMMARY

Hormonal contraception is known to precipitate or perpetuate depression in some patients. The link between oral contraceptive pills and depression relates to the amount and type of progestogen contained in these pills.

Many of the older oral contraceptive pills, which contain ethinylestradiol, are linked to severe mood problems. Newer oral contraceptive pills containing physiological forms of oestrogen may be better tolerated with a purported weaker link to mood problems.

Clinicians should consider the temporal relationship between the use of hormonal contraception and development of new or worsened depression or mood changes.

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Introduction

There are several different forms of contraception available for women. Some of these contain progestogen alone and others contain both oestrogen and progestogen.

There are several forms of long-acting progestogen-only contraception available, including levonorgestrel-releasing intrauterine devices, subdermal implants that release etonogestrel, and medroxyprogesterone acetate intramuscular injections. There are also three different types of progestogen-only pills (Table 1).

Combined contraception is available as a vaginal ring, but combined oral contraceptive pills are the most common form of contraception for women of reproductive age. These contain synthetic analogues of oestrogen and progesterone, which prevent pregnancy by acting locally on reproductive organs and centrally impeding the hypothalamic–pituitary–ovarian axis. Typically, the oestrogen component of oral contraceptive pills contains 20–50 micrograms ethinylestradiol, although newer oral contraceptive pills contain physiological forms of oestrogen such as estradiol and estradiol valerate. The progesterone component is usually a 19-nortestosterone derivative, such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestronol, norethisterone, norethisterone acetate, norgestimate or norgestrel.

The high efficacy and ease of use of oral contraceptive pills make them very popular. However, there are physical and psychological adverse effects. While the physical risks of the oral contraceptive pill are well established,[1] the psychological adverse effects are not as well described.

Effects of oestrogen and progesterone on mood

Oestrogen and progesterone influence neurochemistry, brain function and the activity of neurotransmitters gamma-aminobutyric acid, serotonin and dopamine.[2] Oestrogen receptors (ER)-alpha and ER-beta are widely distributed in the brain, with ER-alpha mainly found in the hypothalamus, hippocampus, amygdala and brainstem. Progesterone receptors alpha and beta are most abundant in the amygdala, cerebellum, cortex, hippocampus and hypothalamus.

There is evidence to suggest that oestrogen is neuroprotective in the hypothalamus, hippocampus, amygdala and brainstem, protecting the brain from neurodegenerative disease, cognitive decline and affective disorders.[3-5] Functional brain imaging studies have indicated that oestrogen regulates the activation of brain regions implicated in emotional and cognitive processing such as the amygdala and

Table 1 **Progestogen-only hormonal contraceptives**

Progestogen	Progestogen content	Brand name
Levonorgestrel, oral	30 micrograms	Microlut
Levonorgestrel, intrauterine device	19.5 mg	Kyleena
	52 mg	Mirena
Norethisterone, oral	350 micrograms	Noriday 28
Drospirenone	4 mg	Slinda
Medroxyprogesterone acetate, intramuscular injection	150 mg	Depo-Provera

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dorsolateral prefrontal cortex.[6] In animals, oestrogen has been shown to modulate neurotransmitters including serotonin,[7] dopamine[8] and noradrenaline in depression,[9] as well as adrenocorticotropic hormone.[10]

Unlike oestrogen, progesterone is not neuroprotective. Progesterone can worsen mood symptoms.[11-13] Plausible links include progesterone augmentation of GABA-induced inhibition of glutamate transmission,[14] and progesterone increasing the concentrations of monoamine oxidase, resulting in decreased serotonin concentrations.[15]

A large study showed a positive association between the use of a levonorgestrel-containing IUD and depression, anxiety and sleep problems in women who did not have these conditions before use of the IUD.[16] There are two formulations of progestogen-releasing IUDs, containing 19.5 mg and 52 mg of levonorgestrel. The former may be more tolerable in terms of mood, as it releases small amounts of levonorgestrel. However, there are no data yet on the relationship between its use and the development or exacerbation of depression.

Common effects of oral contraceptive pills on mood

There is evidence to suggest that both oestrogen and progesterone influence brain function, which may be responsible for the negative mood changes and depression commonly reported in women taking oral contraceptive pills.[17-19] One of the most common reasons given for the discontinuation of oral contraceptive pills is changes in mood or an increase in depressive symptoms.[20,21] Currently, all oral contraceptive pills may cause mood changes, but the newer oral contraceptive pills containing estradiol or estradiol valerate may be less likely to cause mood changes.

The mechanism underlying how oral contraceptive pills influence mood remains controversial. Nonetheless, there is mounting evidence suggesting a significant relationship between taking oral contraceptive pills and lowered mood and mood disorders such as depression.[20,22-25] A comprehensive review published in 2002 included 13 controlled studies investigating the relationship between mood and oral contraceptive pill use.[26] All but one study found differences in affect between oral contraceptive pill users and non-users. Another pilot study involving 58 women found that current oral contraceptive pill users or recent users had higher subjective and objective depression rates than those of non-users.[27] Moreover, a large Danish study involving more than one million women found an increased risk for first use of an antidepressant and first diagnosis of depression among users of different types of oral contraceptive pills, with the highest rates among adolescents.[11] Furthermore, users of medroxyprogesterone acetate, an injectable progestogen contraceptive, reportedly have greater depressive symptoms than those in non-users.[17] The link between taking oral contraceptive pills and depression may be attributed to the amount and type of progestogen contained in oral contraceptive pills (Table 2).

Given that there is a link between hormonal contraception and negative mood or depression, caution must be taken in women who have a personal or family history of depression. However, oral contraceptive pills may provide relief from depressive symptoms in women with premenstrual dysphoric disorder by stabilising the fluctuations in hypothalamic–pituitary–gonadal steroid production.[28,29] In this disorder, the regular use of an active oral contraceptive pill (without seven days of placebo pills) has an antidepressant effect.

Emerging research: nomegestrol acetate with 17-beta estradiol

Currently, all available oral contraceptive pills affect mood. We have shown that nomegestrol acetate (1.5 mg) with 17-beta estradiol (2.5 mg) is better tolerated by women with mood disorders.[30] Our pilot study was a single-site clinical follow-up study that assessed the tolerability and subjective mood response to nomegestrol acetate 17-beta estradiol. Based on a sample of 49 women, we showed that women report a positive mood response and reduced self-reported overall DASS-21 score after taking nomegestrol acetate with 17-beta estradiol compared to previously used oral contraceptive pills.[30] Future research with a larger sample is required.

Nomegestrol acetate with 17-beta estradiol is a monophasic preparation with an extended regimen of 24 active pills followed by four placebo pills. The drug can cross the blood–brain barrier, interact with serotonin receptors and regulate cerebral blood flow to the amygdala, dorsolateral prefrontal cortex and many other areas of the brain involved in depression.[31] Women who develop depression soon (usually between 4 and 12 weeks) after taking other oral contraceptive pills (especially older oral contraceptive pills) may better tolerate nomegestrol acetate with 17-beta estradiol. This is consistent with its successful use in clinical practice for the off-label treatment of mood symptoms associated with premenstrual dysphoric disorder.[30]

Table 2 **Progestogen and oestrogen content of oral contraceptive pills**

Progestogen	Oestrogen	Quantity*	Brand names
Levonorgestrel (micrograms)	**Ethinylestradiol (micrograms)**		
100	20		Femme-Tab ED 20/100, Microgynon 20 ED, Microlevlen ED, Loette, Lenest 20 ED, Micronelle 20 ED
150	30		Femme-Tab ED 30/150, Levlen ED, Microgynon 30 ED, Monofeme, Nordette, Evelyn 150/30 ED, Eleanor 150/30 ED, Micronelle 30 ED, Lenest 30 ED
125	50		Microgynon 50 ED
50	30	6 tablets	Logynon ED, Trifeme, Triphasil, Triquilar ED
75	40	5 tablets	
125	30	10 tablets	
Norethisterone (micrograms)	**Ethinylestradiol (micrograms)**		
500	35		Brevinor, Norimin
1000	35		Brevinor-1, Norimin-1
500	35	7 tablets	Improvil 28 Day, Synphasic 28
1000	35	9 tablets	
500	35	5 tablets	
Desogestrel (micrograms)	**Ethinylestradiol (micrograms)**		
150	30		Marvelon 28, Madeline
Gestodene (micrograms)	**Ethinylestradiol (micrograms)**		
75	30		Minulet
Drospirenone (mg)	**Ethinylestradiol (micrograms)**		
3	20		Yaz, Yaz Flex
3	30		Isabelle, Petibelle, Yasmin
Cyproterone acetate (mg)	**Ethinylestradiol (micrograms)**		
2	35		Brenda-35 ED, Carolyn-35 ED, Diane-35 ED, Estelle-35 ED, Jene-35 ED, Juliet-35 ED, Laila-35 ED
Dienogest (mg)	**Ethinylestradiol (micrograms)**		
2	30		Valette
Dienogest (mg)	**Estradiol valerate (mg)**		
0	3	2 tablets	Qlaira
2	2	5 tablets	
3	2	17 tablets	
0	1	1 tablet	
0	0	2 tablets	
Nomegestrol acetate (mg)	**Estradiol (mg)**		
2.5	1.5		Zoely

* For products with multiple phases of active ingredients

Suggestions for prescribing hormonal contraceptives

The initial decision for prescribing involves a discussion with a woman to determine her preference. The woman's age, general health, past contraceptive use and experience, and reliability in terms of daily pill adherence are usually discussed. The woman's mental health should be discussed in detail in view of links between depression and some contraceptives. This is often ignored and unfortunately can lead to poor outcomes in women.[32] Any history of premenstrual depression or depression related to previous contraception should be carefully noted.

Progestogen-only contraceptives should be used with caution in women with current or past depression.[11] However, if there is a major contraindication for oestrogen-containing contraceptives, a low-dose progestogen IUD or barrier contraceptives may be options.

Healthcare practitioners must recognise the impact of gonadal hormones on mental health and validate their patients' observations, thus promoting a good therapeutic relationship. Weight gain and depression appear to be the main issues that drive changing oral contraceptives. Outcomes are likely to improve with shared decision making for the trial of a particular contraceptive, noting that a change may need to be made after approximately three months. Poor outcomes can occur when practitioners deny a woman's observed relationship between depression, anxiety symptoms and the oral contraceptive.

Conclusion

General community education and better information are urgently needed for primary healthcare practitioners regarding the relationship between oral contraceptive pills and depression. Progestogen-only contraception (Table 1) seems to create a greater propensity for depressive disorders in vulnerable women. Further research is required to determine why some women experience hormone contraceptive-precipitated depression and anxiety, while many women taking hormone contraceptives do not experience mental health issues. It is critical for clinicians to consider the history given by many women of a clear temporal relationship between starting or using a hormone contraceptive and the development of new or worsened depression. In such cases, exploring different types of contraceptives, including barrier methods, is an important patient-validating and therapeutic discussion. ◀

Conflicts of interest: none declared

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