REVIEW ARTICLE

EFFECT OF HORMONAL CONTRACEPTION ON DEPRESSION IN WOMEN

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ABSTRACT

Oral contraceptives are the most frequently chosen method of preventing pregnancy in Poland. Mood changes are one of the most common reasons why young women quit therapy. Depression is a severe disorder that affects millions of people around the world. Some long-term studies suggest an increased relative risk of antidepressant use during contraceptive use compared to non-users. Scientists note an increased risk of suicide as well. Other researchers suggest that there is insufficient evidence to support these findings. Some indicate strong correlation between most hormonal contraceptives and following usage of antidepressant drugs in female adolescents. There is still no consensus in the scientific community. Analyzes of many studies provide ambiguous information. Large-scale studies with properly selected test groups and particular therapies taken into consideration are required in order to accurately assess the risk of depression and mood disorders. In this article, we try to present different approaches to the subject of effects of various types of hormonal contraception methods on depression in women.

KEY WORDS: hormonal contraception, depression, estradiol, progestins

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INTRODUCTION

Almost 10 million women use oral contraceptives (OC) in the United States. 25.3 % of women determined to prevent pregnancy chose OC [1]. It is also the most common method in Poland [2].

The main goal of OC is to prevent ovulation and implantation of the ovum. It also thickens the cervical mucus. Ethinylestradiolum reduces the frequency of menstrual bleedings, blocks the growth of ovarian follicles and prevents ovulation.

Combined hormonal contraception has been proven to be effective – Pearl Index between 0.1 and 0.8. For minipill the values are between 0.5 and 5, which also proves high efficiency. The Pear Index for 52 mg levonorgestrel IUD (Intra Uterine Device) is very high – from 0.09 to 0.11, but IUD with 13.5 mg of levonorgestrel has a 0.33 ratio.

According to a WHO report from 2020 more women than men are affected by depression. One in eight females during her life will suffer from depression. The illness may occur at various ages but most often the symptoms appear in patients aged 40 or older. Twice as many women than men get depressed. According to WHO estimates approximately 350 million people all around the world might be affected by depression which is 5-6% of world population [3].

Relying on data from Institute for Health Metrics and Evaluation (IHME) of Washington University in 2017 2.8 % of Poles suffered from depression which is 0.36 percentage point more than in 2012. Compared to other EU countries Poland had the lowest percentage of clinically depressed patients. However NFZ (Polish National Health Fund) emphasized that data from each country may differ depending on mental health awareness. Citizens of countries with lower stigmatization of ill and better access to specialist care are more likely to seek for it and get included in official statistics [4].

From 2013 to 2018 an increase of patients under 18 and over 65 treated for depression was noted in Poland. In 2018 2.1% of patients were underage and 97.9% – adults. 73% of people undergoing treatment were women [5].

THE AIM

The aim of our work is to present different approaches to the subject of effects of various types of hormonal contraception methods on depression in women.

REVIEW AND DISCUSSION

According to Alicia A. Walf and Cheryl A. Freye estradiol (E2) has various effects on the central nervous system

[6]. Antianxiety and antidepressant-like effects may depend upon many factors, like the regimen of E2 administration and interactions with the hypothalamic-pituitary-adrenal axis. Brain targets for estradiol's effects on anxiety and depression include the hippocampus and amygdaloid body. Administration of E2, compared to placebo, subcutaneously or to the hippocampus or amygdaloid body of rats after ovariectomy decreases anxiety and depressive behavior. Estrogen receptor (ER) antagonists in the hippocampus (but not amygdala) increase those effects of naturally susceptible female rats. Studies on mice suggest that anxiety and depressive behaviors may require estrogen receptors β. It is important to investigate alleged mechanisms and brain targets for estradiol to establish, if it is possible to enhance mood without proliferative effects in reproductive tissues.

The influence of hormonal levels on mood changes in women was also researched by Baca Garcia and associates. The researchers observed higher suicide rates in women during luteal phase in comparison to follicular phase [7].

Frequency of premenstrual dysphoric disorder (PMDD) varies between 1.2 and 6.4% [8]. Women affected by it experience predictable and cyclic psychological, behavioral and somatic symptoms which escalate in late luteal phase and disappear during menstruation. They repeat throughout most fertile years. Patients reported resolution of symptoms after suppression of endogenous ovarian hormone secretion with gonadotropin-releasing hormone (GnRH)-agonist treatment or hormonal contraception. Subjects were studied both during early and late luteal phase in the same menstrual cycle. 63 women with PMDD and 53 healthy participants were included. The PMDD group had significantly lower estrogen levels in comparison to the control group in early ($p < 0.001$) and late ($p = 0.026$) luteal phase. Further analysis indicated that PMDD patients had a higher progesterone level in luteal phase than women from the control group. Those findings show that progesterone induced symptoms of premenstrual dysphoric disorder especially in women with lower levels of estrogen in the early luteal phase.

EFFECT OF PROGESTINS ON DEPRESSION

Theresa A. Lawrie and associates conducted research in which, compared with a placebo group, women receiving a progestin injection (norethisterone enanthate depot given within 48 hours after delivery) were significantly more likely to develop symptoms of depression within six weeks of delivery [9]. Two scales were used to assess symptoms of depression, MADRS (Montgomery-Åsberg Depression Rating Scale) and EPDS (Edinburgh Postnatal Depression Scale). Relative risk (RR) of scores >9 in MADRS and >11 in EPDS for women in the progestin group in the six weeks interview was 2.556 (95% CI 1.262–5.175) and 3.035 (95% CI 1515–6.080). The disadvantage of this study is that the follow-up period is too short, only 6 weeks.

Worly's team identified 26 studies in which there was a minimal association between methods that use progestins alone and depression [10]. There was no correlation with depression in five studies with progestin-based implants and in four out of five studies with levonorgestrel IUDs. After three attempts of intramuscular injection of medroxyprogesterone acetate researchers found no difference in the incidence of depression. For two progestin-only setups, studies show no worsening of depression, while one study has found an association between different forms of progestin-containing contraception and depression.

No effect on mood change in young women using depot medroxyprogesterone acetate as a form of contraception was demonstrated in a prospective study conducted on 63 patients by N.Gupta et al. [11].

Franca Fruzzetti and Tiziana Fidecicchi [12] report that there is no strong evidence to prove a connection between hormonal contraception (HC) and depression. They studied the influence of the progesterone on the neurotransmitters, especially the GABA pathway. They believe the undesirable influence on the mood affects only adolescents or women with a history of affective mood disorder. In that case, the authors suggest using progestogens without androgen or anti- androgen effects.

Slattery et al. conducted a study in order to determine if levonorgestrel administered through an intrauterine device increases the risk of anxiety, panic attacks, sleep disorder, restlessness and if so, to what extent [13]. To achieve this researchers used data of THIN database from Great Britain. They found a connection between exposure to levonorgestrel and increased risk of anxiety (hazard ratio = 1,18; 95%) and insomnia (hazard ratio = 1,22; 95%) in women without a prior record of these events. They established no relevant connection with panic attacks or restlessness.

EFFECT OF TWO-COMPONENT DRUGS

Another analysis [14] shows a significant mood improvement in women taking oral contraceptives with levonorgestrel and ethinylestradiol for 3 months. This was a double blind, randomized, placebo-controlled study and the main outcome measure was PGWBI (Psychological General Well-Being Index).

Cecilia Lundin and her team [15] noticed a negative influence of hormonal contraception usage on mood only during the intermenstrual phase. Previous studies focused on proving the positive effects during premenstrual phase and menstruation. It's the time when most women experience problems like painful menstruation, premenstrual syndrome, premenstrual dysphoric disorder. A lot of them expect the reduction of the symptoms by hormonal contraception [16]. Results of this randomized and controlled study suggest that taking combined oral contraceptives (COC)-containing 1.5 mg E2 and 2.5 mg nomegestrol acetate – induces mild, but significant side effects. Intermenstrual phase (according to this study) lasts from day 5 of the cycle until day 21. The biggest differences have been noted between day 6 and day 9 of the cycle- when women taking placebo had late follicular phase. In this phase women taking placebo were exposed to increased estrogen levels until it reached the preovulation level. Lower concentration of endogenous estradiol or continuous exposure to COC might have affected the results of the study.

According to Neri et al. [17], tablets with 17-beta estradiol and nomegestrol acetate have a positive effect on the mental state of women. In a prospective observational study from 2017, anthropometric indicators and body composition parameters were analyzed, as well as symptoms related to the menstrual cycle and mental well-being. Improvement was observed in the last two categories, with no effect on the anthropometric parameters.

Shen suspects that adolescent girls may be more susceptible to the effects of exogenous hormones. An interesting discovery, although confirmed only on an animal model, is that female mice respond differently to allopregnanolone during puberty. Increased activity of the α4βδ GABAR at the beginning of adolescence promotes increased anxiety reactions [18]. Another reason may be found in the social relationships of teenage girls using hormonal contraception. Early sexual initiation has been associated with and increased risk of depressive symptoms and decreased self-esteem [19]. Scientists also stated that teens with depression were more likely to choose the IUD as a method of contraception [20].

COMPARISON OF CONTRACEPTIVE METHODS

In 2016 Charlotte Wessel Skovlund's team published the results of a prospective cohort study involving over one million women living in Denmark. Data was collected from 1995 to 2013 [21]. The study group excluded those women who had already used antidepressants before 1995, as well as those who could not use them for health reasons. Danish researchers observed an increased risk of the first use of antidepressants during therapy with any type of hormonal contraceptive. One of the groups consisted of women using progestogen pills – relative risk 1.34 (95% CI 1.27-1.40). The relative risks of women using IUDs and transdermal patches were higher than those using the tablets, however the authors of the study associate this with a higher dose rather than with the route of drug administration. Additionally, it was noted that the analyzes limited to adolescents (15-19-years-old) showed a higher relative risk of starting antidepressant use and of first diagnosis of depression. Compared to those not treated with hormonal contraception, the relative risk for combined oral hormonal contraception was 1.8 (95% CI 1.75-1.84). With age, the relative risk of depression decreased. There was a correlation between the duration of hormonal contraception therapy and the relative risk of using antidepressants and the diagnosis of depression. Relative risk was highest after 6 months and then decreased (however, it was still higher compared to non-users – only after 4 years of treatment, relative risks were ~ 1).

Another analysis on the same study group assessed the relative risk of suicide attempts and suicide while using hormonal contraception [22]. Compared to women who had never used hormonal contraception, the relative risk of a suicide attempt was 1.97 (95% CI = 1.85-2.10) and for suicide was 3.08 (95% CI = 1.35-7.08). Suicide rates were highest after 2 months of drug use. The highest relative risks were observed in young female patients.

Bloch and associates noticed that changes in the ovarian hormones concentration are more important than the absolute level of hormones in the pathogenesis of mood deterioration. Menstruation, menopause, pregnancy and labour are the factors that allow depression to develop. [23].

Abrams analyzed the results of 119 women using a single-phase, three-phase or non-hormonal method of contraception [24]. For three months, the assessment of at least two complete menstrual cycles was performed. Patients using parenteral hormonal contraception reported fatigue, sadness, and deterioration of mood at the end of the cycle slightly more often. However, the difference was not significant and the researchers emphasize the lack of clinical relevance. Researchers connect this phenomenon to PMS, not to the influence of hormonal contraception on the mood of patients.

In a study conducted on over 75,000 women, the relationship between the use of hormonal contracep-

tion and the following use of antidepressants or the diagnosis of depression during the first 12 months after childbirth was assessed [25]. Less than half of the surveyed women (41.7%, n = 31506) started using hormonal contraception within 12 months after childbirth. Norethindrone-only tablets accounted for 63.1% of contraceptive initiation (n = 19,883), levonorgestrel-containing intrauterine systems 9.8% (n = 3096), etonogestrel subcutaneous implants 8.7% (n = 2730), ethinyl estradiol / norgestimate tablets 8.6% (n = 2718), ethinyl estradiol / norethindrone 5.3% tablets (n = 1675) and ethinylestradiol / etonogestrel vaginal rings 4.5% (n = 1404). The percentage of women taking antidepressants in the first year postpartum was 7.8% (the Keplan-Meier estimation). Studies have shown a connection between the use of hormonal contraception and subsequent depression and the use of antidepressants, however, this relationship has not been assessed in postpartum women.

Another research on women after childbirth shows a significant connection between hormonal contraception and depression [26]. Women (n=242) were randomly assigned to two groups. First group received DMPA (medroxyprogesterone acetate) and the second group received an intrauterine device containing copper 48 hours after labor. Patients were examined in the first and second month after delivery. Scholars used Beck Depression Inventory (BDI-II) and Edinburgh Postnatal Depression Scale (EPDS). EPDS results after the first month were significantly higher when women used DMPA than in the intrauterine device group. According to BDI-II results more women using DMPA had severe depression at months 1 and 3 than in the other examined group.

A LINK BETWEEN CONTRACEPTION AND DEPRESSION IN ADOLESCENTS

McKetta and Keyes from the USA were looking for a link between usage of oral contraception and depression among female adolescents in National Comorbidity Survey Adolescent Supplement [27]. 4765 teenage women who reported current or previous oral contraception (OC) usage and no history of pregnancy were included in the study. They also reported the age of OC initiation. Previous and current depression episodes were included. It was stated that using OC does not cause increased risk of depressive disorders. Lack of influence on depression or worsening of previously present depressive state was also established in prospective study on a group of 39 adolescent women who had been using depot medroxyprogesterone acetate (DMPA) for 12 months.

Discontinuation rates of HC are high, especially among adolescents, and mood complaints are one of the most frequently mentioned reasons for treatment discontinuation.

Research among women aged 12-30 was conducted [28]. They were observed since first usage of hormonal contraceptives for the whole year or up to the point when they started taking antidepressants. Among HC users the absolute risk of using antidepressants was around 4% for all age groups. However, in young non-users of HC the risk was very low and increased in age up until age of 21 or older. At that age the risk reached the level of HC users. The results indicate strong correlation between most hormonal contraceptives and following usage of antidepressant drugs in female adolescents without previous psychiatric morbidity. The highest odds ratio were noticed in 12 to 14 year old girls using intravaginal rings or skin patches containing progesterone. This connection was permanent and high for most types of HC in adolescents but was lower or disappeared in women over 19. The influence of HC on mental health might vary due to personal traits, disorders such as premenstrual dysphoric disorder (PMDD), dysmenorrhea or different susceptibility to neuroactive metabolites of progesterone.

CONCLUSIONS

Despite of the reported dependencies between use of hormonal contraceptives and increased risk of depression in women, the evidence still remains ambiguous. More large-scale studies with properly selected test groups and particular therapies taken into consideration are required in order to accurately assess the risk of depression and mood disorders. Shaffir's team [29] in 2016 described problems concerning those studies: lack of prospective studies, various methods of examining mood swings and the fact that researchers are adding women who take different types of contraception to one cohort.

While oral contraception is being commonly used, problem of depression occurrence and its relation to hormonal therapies remains underestimated. Depression belongs to disorders with multifactorial genesis. Detailed patient history regarding depression episodes should be obtained by doctors prescribing hormonal medications. On the other hand psychiatrists should take into consideration the possible effects of oral contraceptives on the mood changes and depression incidence. Hormonal contraception cannot be treated as an "on demand" therapy, but the patients should be informed in details about all the possible adverse effects to make a conscious decision.

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