Association of Hormonal Contraceptives with Depression among Women in Reproductive Age-Groups- a Cross-Sectional Analytic Study

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Article

Association of Hormonal Contraceptives with Depression among Women in Reproductive Age-Groups- A Cross-Sectional Analytic Study

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* Correspondence: sssultan@fcms.edu.sa

Abstract: Objective-Most women stop using hormonal contraceptives due to changes in their mood. The evidence regarding the association of hormonal contraception with depression shows mixed results. Therefore, we aim to establish the association between the use of hormonal contraception and depressive symptoms**. Method-** This cross-sectional study was conducted on 326 women of reproductive age using hormonal contraceptives for a week to one year referred to as "hormonal contraceptive (HC) users" (n=165), and those using non-hormonal methods and not using contraceptives referred to as "HC non-users" (n=161). Beck's depression inventory (BDI-II) was used to measure depression. **Result-**There was no discernible difference in mean Beck's depression inventory score and degree of depression between the two groups. However, individual symptoms of depression such as sadness(p=0.01), reduced libido(p=0.0002) feelings of pessimism (p=0.02), and failure (p=0.003) were found to be significantly high in the HC user group. **Conclusion-** We conclude that there was no significant difference in mean depression scores between groups. However, few individual symptoms of depression were high in HC users suggesting depression as a potential side effect of hormonal contraceptive use.

Keywords: hormonal contraceptives; oral contraceptives; contraception; depression; major depressive disorder

Introduction

Oral contraceptive pills (OCP) are the most commonly used contraceptive measure, owing to their effectiveness and practicability.[1] The estimated use of OCPs ranges from 45% to 64% in the Kingdom of Saudi Arabia [2].

Oral contraceptive pills (OCPs) is often used by women to prevent pregnancy or address menstrual symptoms. However, 32-60% of the women discontinue the use following 6 months for a variety of reasons, including mood changes [3]

HC has a mixed effect on mood, ranging from improved mood [4–6] to worst mood [7–14] or has no effect at all [13,15] These findings suggest that some women may benefit from HC use, while others do not or even have negative impact. Most studies have discovered a connection between teenage use of hormonal contraception and an increased risk of developing depression [7–10,14]. The impact of hormonal contraception on adult depression risk is less clear; some sources contend there is either no increased risk or a decreased risk in adults [6,13]. Nevertheless, a meta-analysis of 15 randomized controlled studies failed to detect a link between HC use and depressive symptoms [15].

A Danish study of over a million women indicated that all hormonal forms of contraception increased the risk of depression across all age categories, with teens having the highest risk of depressive symptoms [8]. The use of hormonal contraceptives was found to be positively associated with the use of any form of psychotropic drug in a Swedish survey of 800,000 women, although only among adolescents [9]. Another study of over 900,000 Swedish women found increased antidepressant use among adolescents on different types of OCPS while in adults this association was

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only observed with progestin-only pills [10]. The majority of studies, however, indicate that mood instability brought on by HC use is transient: Skovlund et al. showed that the largest correlations between HC use and depression occurred in the first 6–12 months after HC was started [8].

The heterogeneity in the above-described findings can be attributed to the difference in the study population, varied questionnaires (unvalidated) used to assess depression, and multiple confounders. However, few randomized clinical trials revealed that OCP improved depressive symptoms while increasing mood swings and irritability [16,17]. Literature shows mixed findings about the relationship of HC with depression. Therefore, we aimed to examine the association between HC use and concurrent depressive symptoms. The objectives of the study are 1. Analysis of depressive symptoms in HC group versus control group. 2. relation of depression scores to the duration of HC use and type of contraception. 4. Determining which depressive symptoms are more commonly seen in HC users.

Methods

Study Design and Setting

This Analytic cross-sectional study was conducted from November 2022- August 2023. The study was conducted after ethical approval from the institutional review board.

Sample size and sampling strategy

Taking the prevalence(p) of depression as 33.3% among women using contraceptives from a previous study from Saudi Arabia [35], at 95% confidence interval(Z) and taking the margin of error(d) as 5%, the sample size was calculated using the below formula:

Sample size, n = DEFF*Z2 1-α/2p(1-p)/d2 where DEFF=1, Z=1.96 p=00.33 and d=0.05

The sample size came to 342. A total of 326 non-pregnant women in the reproductive age group of 15-49 years were included in the study by employing consecutive sampling techniques. Participants with a diagnosis of depression or use of psychiatric medication in the past, family history of depression, and chronic physical illness were excluded from the study. Data was collected by face-to-face interviews using a pretested semi-structured questionnaire consisting of socio-demographic factors, clinical characteristics, and BDI-II

Measurements

Data Collection Sheet

A data collection sheet was used to record information about age, education socioeconomic status, living problems, social support, relationship problems, duration of HC use, and type of HC used (combined [estrogen and progesterone] or progesterone only). This was prepared by researchers after reviewing similar related articles. A pilot study of 20 participants was done to check the reliability of the questionnaire (Cronbach's alpha=0.83).

Beck's Depression Inventory-II

Beck's depression inventory-II (BDI-II) was used to measure the outcome (depression). The BDI-II is a widely used 21-item scale that can be used by a trained interviewer or self-rated· BDI-II is used both in clinical practice and in research to assess the level of depression in patients and also in healthy persons with good validity and reliability. The items rating is on a 4-point Likert-type scale (0-3 points per item). The severity of symptoms is interpreted as "normal" (1-10). "mild" (11-16), "borderline clinical depression" (17-20), "moderate" (21-30), and "severe" (31-40) and extreme depression (>40)[18]·

Study Procedure

The survey was conducted at Dr. Soliman Fakeeh Hospital on a total of 326 non-pregnant women in the reproductive age group who visited the family planning unit of the obstetrics and gynecology department and came to the hospital pharmacy for a refill. Written informed consent was

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taken from all participants. The information about age, sociodemographic details, day of the menstrual cycle, type of OCP and duration of its use was recorded on the data collection sheet by the trained interviewers (6th-year medical students). Subsequently, the interviewers used the BDI-II to assess depression in the subject and give the appropriate score.

Statistical Analysis

Descriptive statistics were performed for sample characteristics. Continuous variables were summarized as means with their standard deviations whereas qualitative variables were summarized by frequency and percentages. The unpaired t-test was used to compare two continuous variables and the chi-square test/Fisher exact test was applied to compare two proportions. P value of less than 0.05 was taken as statistically significant.

Result

A total of 326 women in the reproductive age group of 15-49 years with no previous or family history of depressive disorder were included in the study. Women participants using hormonal contraceptives currently for the past one week or more were taken as "Hormonal contraceptives (HC) users" and those using any non-hormonal methods and not using any contraceptives were taken as "HC non-users". Out of 326 women included, 165 were HC users and 161 were HC non-users (non-hormonal =49 and no contraceptives= 112). Their detailed sociodemographic and clinical profile is demonstrated in (Table 1).

Of 326 participants 51% used hormonal contraceptives, 34% were non-users and 15% used non-hormonal contraceptives- The overall prevalence of any method of contraception was 65.7%(n=210) among the study participants. Amongst the sample, 50.6% (n =165) reported hormonal contraception use, while 15.0% (n = 49) reported using non-hormonal methods (Figure 1). Among hormonal methods, 28.8% and 13.8% of the women reported using combined estrogen and progesterone and progestin-only pills, respectively, making OCPs the most used method. As for non-hormonal methods, Copper IUDs ranked highest in percentage (9.2%) (Table 2). The mean Beck's inventory score of the participants was 9.86±8.21 with scores ranging from 0 to 63. A total of 200(61.3%) participants were normal, 65(19.9%) had mild mood disturbances, 28(8.6%) had borderline clinical depression, 24(7.4%) had moderate, 8(2.4%) had severe and 1(0.3%) had extreme depression (Figure 2). Participants who self-rated their health as poor has also shown significantly higher clinical depression (p=0.00001) (Table 3).

There was no discernible difference in mean BDI score and degree of depression between the two groups (Table 4). A comparison of degrees of depression between HC users and non-users is shown in Figure 2. On Comparing oral pills and other hormonal contraceptives about depression status, no significant difference was found. Similarly, the duration of hormonal contraceptive use was also not found to be associated with the degree of depression (Table 5). However, the use of HC was associated with significantly more sadness(p=0.01), reduced libido(p=0.0002) feelings of pessimism (p=0.02), and failure (p=0.003) (Table 6).

Discussion

This study examined the association between the use of HC and depression among Saudi women in the reproductive age group. We found no significant difference in mean BDI score and degree of depression between the two groups. Our findings are consistent with several observational studies [6,7,14] and RCTs [15,17] which found no association between HC use and depression. According to a 2013 study that used data from the National Longitudinal Study of Adolescent Health, OCP use shielded US women between the ages of 25 and 34 from depressive symptoms [7]

Our results are at odds with earlier studies that found using medication registry data that OCP use increased the likelihood of antidepressant use [8,10]. Skovlund et al. [8] discovered data from the Danish drug registry that suggested a considerable positive correlation between OCP usage and anti-depressant use especially among the youths. In their sample, current OCP users had an RR of anti-

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depressant use of 1.8 in comparison to non-users. [8]. Skovlund et al. [8]looked at both antidepressant use and medical discharge coding for depression and discovered that there was a substantially weaker correlation between the two, indicating that antidepressant use is a poor proxy for an actual depression diagnosis. Both medical coding for depression and using antidepressants necessitate contact with a medical provider, leading to the potential risks of surveillance bias or confounding by indication. Similarly, a Swedish study [9] reported that HC users had an adjusted OR of first-time use of psychotropic drugs of 1.34 with particularly high odds ratios (OR-3.36) in 12- to 14-year-old girls. Both these studies found a high risk of antidepressant consumption in teenagers and in those using progesterone-only HC [8]. Interestingly, non-oral progesterone methods such as depot medroxyprogesterone acetate (DMPA) injection, skin patches, and intravaginal rings showed more depression when compared to oral progesterone pills [6,9,10]. A longitudinal cohort analysis of 740,000 women based on data from six Swedish Prescribed Drug Registers found no overall increased risk of depression, except a modest increase in risk in the adolescent age group. The major strengths of this study were its sample size, longitudinal design, adjustment for confounders like smoking, BMI, and past and family history of mental disorders. Additionally, recall bias was non-existent as the data was based on ICD codes [6]. According to Anderl et al.,[11] women who started using oral contraceptives (OCs) in their adolescence had a higher 1-year prevalence of depression compared to women who never used OCPs or who started using them in their adult years. This study had potential confounders such as recall bias and lack of information regarding the duration of use and type of OCP used.

Most studies found an increased risk of depression in the adolescent age group as compared to adults [7–10,14]. One convincing reason for the positive results could be attributed to confounders such as age at sexual debut, smoking, BMI, education, chronic health conditions, and social and behavioral factors. We believe that precocious sexual behavior and drug use are linked to an increased risk of taking OCP as well as an increased chance of developing depressive illness, which may affect these findings. It has been found that early sexual initiation is linked to increased risks of destructive behavior and poor mental health [19]. Because HC use is a suitable proxy for an active sex life, the effect of starting HC at a young age may instead correspond to the effect of an early sexual debut. However, the increased risk of depressive symptoms among oral contraceptive users vanished after adjustments for sexual debut and smoking [14]. Another issue is that HC is used not just to prevent pregnancies but also to treat somatic symptoms like dysmenorrhea and PMDD, which may be more prevalent in adolescents and have a negative impact. In a cohort study of women in their 20s conducted in Australia, the connection between HC and depressive symptoms vanished when confounding factors such as non-contraceptive usage of HC were controlled [20]. Depression scores in our study did not vary with age, type of HC, and duration of HC use, unlike previous studies that have shown a high risk of depression in teenage and progesterone-only HC [8,9]. Nevertheless, the biggest limitation of the previous studies and our study is their cross-sectional design. The inclusion of solely married women in the sample could be another explanation for why we did not detect an increase in depression in our research. As sex among unmarried teenage girls was linked to an elevated risk of depression and suicidal behaviors [21], this exclusion could have lessened the confounding effect.

Our findings contradict regional studies that have found a higher frequency of moderate to severe depression in HC users compared to non-users [22,23]. One community-based cross-sectional study of 4853 participants aged between 21- 45years reported a higher frequency of moderate to severe depression in HC users. However, this study had a wide range of confounders, used an online self-reported questionnaire which can lead to sampling and respondent bias, and lacked information about pill formulation, doses, and medication compliance [22]. Another study conducted at Primary health care centers also reported higher depression scores in HC users and moderate and severe depression in those with a history of depression and HC use. The study used a self-administered questionnaire and did not adjust for confounders such as BMI, smoking, past and family history of depression, and chronic medical conditions [23]. Nonetheless, when our study evaluated individual depressive symptoms, we found HC users reported significantly more sadness, feelings of pessimism

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and failure, and reduced libido while other symptoms of depression showed no significant difference. Similarly, a previous study also reported higher scores of depressed mood and mood swings in users of combined oral contraceptive pills in comparison with placebo, and these mood changes were associated with altered reactivity in emotion circuits of the brain especially affecting the insula and inferior frontal gyri and amygdala [24]. Another study demonstrated that mood worsening among individuals using OCPs was more likely in users with a history of depression [25]. This finding may indicate that a subset of depressed women may be more susceptible to mood worsening brought on by OCP due to their heightened sensitivity to the interplay between cycling gonadal steroids and affect. However, our study excluded women with a history of depression and those women who used any psychiatric drug in the past to reduce the confounding effect. Similar to our study few observational studies have suggested that HC users have diminished libido and sexual function [26] while RTCs showed no such link [27]. One may wonder why a feeling of pessimism and failure was associated more with HC users. This could be explained as secondary to the sad mood reported by the HC users or a personality attribute by itself.

Limitations

The cross-sectional design does not allow for mood assessment before pill consumption or identification of a depressive trend during the first several months of administration. To reach an adequate sample size we employed a consecutive sampling strategy which limited the generalizability of our findings. There is a possibility that those who stopped using hormonal contraceptives did not return for review and drug collection at the pharmacy further reducing the real estimate of depression. Moreover, the cross-sectional nature of the study cannot conclude a causal relationship. The interview was conducted by the trained medical students which curtailed the possibility of sampling bias and respondent bias. We consider this as a strength of our study as most previous studies used either online questionnaires or drug registries for the use of psychotropic medications by OC users with no comparison group.

Future prospective longitudinal studies should systematically document the short- and long-term effects of using different types of OCs (and other forms of hormonal contraceptives) on women's mental health; this may also help to identify further the specific biochemical mechanisms underlying the observed association.

Conclusion

We conclude that there was no significant difference between mean BDI scores in the HC user group when compared to the non-HC user group. However, there were significantly increased depressive symptoms such as sadness, decreased libido, and increased feelings of pessimism and failure in HC users. Our findings suggest that depression can be a potential side effect of HC use. Further, longitudinal studies are required to warrant depression as an adverse effect of HC use.

Abbreviations

HC- Hormonal contraceptives**;** OCP- Oral contraceptive pills

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