A Meta-analysis of the Effect of Oral Contraceptive Use
on Women’s Psychological Well-being

An Honors Thesis (PSYS 499)

by

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Abstract

Meta-analysis was used to explore a possible relationship between oral contraceptive use and women's psychological well-being. An analysis of 13 useable studies found a small positive effect of oral contraceptive use on women's psychological well-being. However, the meta-analysis also found great variance among the results of the studies. Possible moderator effects of women's health status and history, type of oral contraceptive, or different hormone combinations of oral contraceptives could explain these results. However, there were too few useable studies to conduct statistical analyses of these possibilities.
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A Meta-analysis of the Effect of Oral Contraceptive Use
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Oral contraceptives are so commonly used and so well known that they have been termed simply "the pill." For example, based on a sample of 12,279 female respondents Jones, Mosher, and Daniels (2012) reported that almost two thirds of women in the United States used some form of contraception between 2006 and 2010; oral contraceptives (OC) were the most common form of contraception with 17% of women reporting OC use. Looking to the future, Murphy (2006) noted a rise in the demand for more easily accessible oral contraception and given the provisions of the Affordable Care Act, which calls for insurers and employers to provide contraception in health insurance plans, the demand for OC's could further increase in the near future (Starr, 2013).

Preventing pregnancy is not a novel concept; through the ages women have used various methods to avoid pregnancy. Although recorded instances of contraception date as far back as 1500 BC Egypt (Chadwick, Burkman, Tomesi, & Mahadevan, 2011), prescribing medication to a healthy patient is a more recent idea. As a consequence, carefully weighing the risks and benefits of oral contraceptives has been and still is important. For example, Chadwick et al. reported that although risks have been reduced in recent forms of OC, side effects such as stoke, hemorrhagic stroke, myocardial infarction, and deep vain thrombosis are still possible. On the other hand, aside from preventing pregnancy, OC is also associated with a long list of benefits including menstrual cycle regularity and reductions in acne, functional ovarian cysts, benign breast disease, ectopic pregnancy, menstrual blood loss, iron deficiency anemia, and dysmenorrhea. Chadwick et al. concluded newer and more effective forms of OC are progressively reducing its physiological risks and its increasing physiological benefits. Although
Chadwick et al. conducted a comprehensive review of oral contraception and its physiological side effects, they did not address potential psychological side effects.

**How Might Oral Contraceptive Use Affect Psychological Well-being?**

Before examining the literature on psychological side effects, it is important to examine the possible mechanisms by which OC might affect psychological well-being. Early researchers leaned towards negative societal and personal attitudes toward contraception as possible causes of adverse psychological effects (e.g., Weissman & Slaby, 1973; Malek-Ahmadi & Behrmann, 1976). When researchers began to examine possible pharmacological causes of psychological side effects, they focused on depression and its negative correlation with serotonin levels (Malek-Ahmadi & Behrmann, 1976). Two possible mechanisms were proposed for how OC affects serotonin. First, OC directly activates tryptophan 2, 3 dioxygenase, converting tryptophan into niacin and lowering serotonin; second, estrogen (a main ingredient of OC) decreases serotonin levels by inhibiting pyridoxal phosphate and reducing vitamin B6 (Malek-Ahmadi & Behrmann, 1976). Maleck-Ahmadi and Behrmann also postulated that progesterone levels in OC may affect mood, although the mechanism was unclear.

As more researchers began to examine the effects of dosage level and composition of OC more closely, they discovered additional mechanisms by which OC could cause psychological side effects (Kurshan & Epperson, 2005). For example, Rapkin, Biggio, and Concas (2006) reviewed the ways in which OC could influence neuroactive steroids levels, noting that the hormones active in OC, mainly estrogen and progestin, decrease production of GABA receptors and other neuroactive steroids. GABA is an inhibitory neurotransmitter that regulates mood, sleep, and cognitive functioning; therefore, a decrease in GABA could affect those functions. Because some women experience mood stabilization whereas others experience adverse mood
changes from OC use, the direction of the effect of GABA inhibition, if any, is unclear. Rapkin et al. called for more research to determine if estrogen, progestin, or both reduce GABA production.

**Previous Literature Reviews**

Although a computer assisted search did not turn up any previous meta-analyses on the relationship of oral contraceptive use to psychological well-being, I found several narrative literature reviews. As early as a decade after FDA approval of OC, researchers compiled information regarding possible effects of contraception on mood (Weissman & Slaby, 1973). Since then, the focus of the research has changed, with early researchers examining OC’s adverse mood effects and more recent researchers examining its mood-stabilizing effects (Weissman & Slaby, 1973; Poromaa & Segebladh, 2011). This section summarizes the findings of those previous literature reviews. As will be seen, despite the large amount of research on the topic, the results of that research remain inclusive on the possible psychological side effects of OC use.

**Early research on the psychological side effects of oral contraceptives.** Weissman and Slaby (1973) conducted the first review of the research on side effects of OC use. They observed that physicians and the general public had believed that oral contraceptives produced a negative effect on women’s psychological well-being from the time the FDA approved them in 1960. However, the results of research on this question were contradictory. From 1943 to 1966, various researchers reported a variety of findings, including a positive association between OC and depression, that OC reduced depression, and that a psychological predisposition associated with depression developed during OC use. Weissman and Slaby further noted that studies conducted from 1968 to 1971 were also unable to provide evidence of a causal relationship between OC and
psychological well-being, specifically depression. Researchers found that OC was associated with depression during the first month of use and diminished after that. In 1969, researchers concluded that depression during OC use was correlated with previous instances of depression. Weissman and Slaby (1973) concluded that the most probable cause of negative psychological effects of oral contraceptive use were negative individual and societal attitudes toward OCs; when the consumer expected negative psychological side effects, she experienced negative psychological side effects. If Weissman and Slaby were correct in this conclusion, the current more positive societal attitude of acceptance of contraception would eliminate instances of depression and negative affect; however, because depression still occurs during OC use, psychological side effects must be pharmacological.

Based on the findings of their literature review, Malek-Ahmadi and Behrmann (1976) agreed with Weissman and Slaby (1973) that any psychological side effects of contraception were most likely a result of expectations for negative effects. However, they also noted that oral contraceptives could disturb tryptophan metabolism in the central nervous system, decreasing serotonin levels, thereby inducing depressive symptoms and that progesterone could contribute to occurrence of depression in OC use. Although they acknowledged these possible pharmacological mechanisms, Malek-Ahmadi and Behrmann nonetheless suggested that adverse psychological effects of OC could result from cultural, religious, societal, or spousal disapproval. Further, they suggested that physicians could prevent or alleviate adverse psychological effects by inquiring about patients’ personality and mental health history before prescribing OC, conducting frequent check-ups when an OC user has a history of depression, explaining OC and its possible side effects, and prescribing daily doses of 50mg vitamin B₆ to offset of possible tryptophan metabolism disturbances.
Hormones and psychological side effects of oral contraception. Bruce and McCauley (1997) focused their literature review on estrogen and progesterone, two components of oral contraceptives that are linked to emotional and mental well-being and so may be linked to side effects such as depression. They reported that although many studies conducted between 1985 and 1995 examined possible relations between fluctuating hormone levels and mood across the menstrual cycle, none produced conclusive results. They noted that researchers also focused on the effect of estrogen and progesterone in oral contraceptives on mood and sexual functioning; however, the results of that research were also inconclusive. Bruce and McCauley also pointed out a change in the focus of research: although earlier research had suggested a positive association between depression and OC, researchers in the 1980’s and early 1990’s suggested that lower-dose OC might improve pre-existing mood state. That research also suggested that although most women do not experience negative affect from low-dose OC, a minority do experience negative affect. In addition, some researchers postulated that negative affect experienced during OC use may be the result of a predisposition to depression. Brace and McCauley described a 1988 twin study that reported a genetic vulnerability to mood disturbances may be involved in OC side effects, although support from research for this hypothesis was inconsistent. Brace and McCauley concluded that an association between estrogen, and therefore oral contraception, and psychological well-being existed although the strength and direction of that association remained inconclusive.

New millennium research on OC and mood. With the dawn of the new millennium, OC research continued to explore the relation of OC use to mood. Oinonen and Mazmanian (2002) provided a comprehensive overview of this research that was conducted from 1967 to 2000. New millennium research proposed that estrogen and progesterone either independently or
together affect GABA activity to lower serotonin levels. In addition, progesterone was possibly connected with increasing monoamine oxidase (MAO) to reduce serotonin levels in OC users. Oinonen et al. classified OC research into categorical and dimensional research: categorical research investigated the occurrence of diagnosable mood disorders while dimensional research investigated daily mood fluctuation. Categorical research included a large amount of early research on OC; as noted earlier, this research variously found that OC increased, decreased, and had no effect on depression rates. Dimensional research included the vast majority of more recent research. Most of this research did not find a significant relationship between OC use and mood, but four studies reported less day to day mood variability in OC users. Oinonen et al. concluded that the results of most research indicated a positive psychological effect of OC, but a history of depression, moderate to severe premenstrual depression, dysmenorrhea, or postpartum depression could put women at risk for negative psychological side effects of OC use, such as depression. Although previous research syntheses had concluded that OC mood effects resulted from negative expectations, Oinonen et al. cited a 1971 study that refuted that possibility.

Oinonen and Mazmanian (2002) also reported results of the effects of different OC dosages. The research they examined showed that high doses of OC were associated with adverse mood effects. Progesterone dosage, in particular, appeared to be related to mood; high doses negatively affected mood, low doses also negatively affected mood in women with a history of PMS, and higher doses of progesterone relative to estrogen dosages produced negative mood effects. In addition, monophasic OC tended to have mood stabilization effects whereas triphasic OC was more likely than mono- or bi-phasic OC to produce adverse mood effects. *Monophasic* OC refers to pills that administer the same dosage of hormones throughout the menstrual cycle while *biphasic* and *triphasic oral contraceptives* change the dosage of hormones
once and twice respectively during a menstrual cycle. Oinonen et al. reported that a major flaw in research on the relation between OC and mood was the "survivor effect" in which women who experience negative psychological effects stop taking OC, resulting in an underestimation of mood effects. Oinonen et al. concluded that research did not eliminate the possibility of indirect roots for psychological side effects, such as expectations of mood change, guilt or security about preventing childbirth, and mood change resulting from physical side effects.

Although indirect causes of psychological side effects are a possibility, Poromaa and Segebladh (2011) concluded from their literature review that research supported the presence of more positive than negative psychological side effects. A change in OC ingredients from progesterone to drospirenone and desogestrel appeared to have resulted in fewer adverse psychological side effects. In addition, lower doses of ethinyl estradiol (EE)/levonorgestrel may be less likely to cause negative mood and more likely to have positive mood effects than higher doses or progesterone-only OCs. Poromaa and Segebladh also found that low socio-economic status African American women who used OC experienced higher levels of positive mood and lower levels of negative mood during stable OC use compared to less pronounced variability in mood during intermittent OC use. In addition, Poromaa and Segelbladh found that mood variability appeared to be correlated with the menstrual cycle: adverse mood was more likely to occur during the pill-free interval and more positive mood during the menstrual and premenstrual phases. Poromaa and Segelbladh, unlike Oinonen and Mazmanian (2002), concluded that OC may benefit women with premenstrual dysphoric disorder and possibly women with major depression, but that further research was needed.

**Oral contraceptives, mood, and premenstrual dysphoria.** Kurshan and Epperson (2005) reviewed research on OC mood effects on women with premenstrual dysphoria (PMDD).
They found that research conducted from 1972 to 2003 offered more support for OC alleviating adverse mood effects than for producing adverse mood effects. The introduction of more androgenic ingredients such as drospirenone into OC and of newer progestins may have accounted for the shift from adverse to positive mood effects and so these newer formulations may be beneficial to women with PMDD; however, Kurshan and Epperson thought that the results of the research were inconclusive on that point. Like Oinonen and Mazimanian (2002), Kurshan and Epperson reported that triphasic OC resulted in more adverse mood effects than monophasic OC in women with PMS symptoms. Therefore, more androgenic doses of OC could be helpful to both healthy women and those with a history of PMDD and PMS symptoms. Kurshan and Epperson concluded that OC is not associated with adverse psychological effects in healthy women, although subgroups may experience negative mood effects.

**Conclusions.** During the history of research on the relationship between oral contraceptive use and mood, the focus has shifted from adverse mood effects to positive mood effects and to whether adverse mood effects differ for different groups of women, such as members of different ethnic/racial minority groups. Changes in the formulation of OC, such as including more androgynous ingredients and lower hormone dosages, accounted for most of that shift in research focus. Research reviewers agreed that monophasic contraceptives result in less adverse psychological effects than biphasic contraceptives and biphasic contraceptives result in less severe psychological effects than triphasic contraceptives. Women with a predisposition for mood disorders, PMDD, or severe PMS symptoms appear to be at higher risk for adverse mood symptoms with most OCs. Further research is needed to determine whether other subsets of women have higher risk of adverse psychological effects, the severity of their increased risk, and any conclusive effects of OC on psychological well-being.
The Current Research

The research discussed above has examined general trends and limitations in oral contraceptive use and psychological well-being. However, prior literature reviews have been qualitative and so have not quantitatively addressed such issues as effect sizes and moderator variables. In addition, some of the research reviews did not include all of the available research articles. The current study will take the form of a meta-analysis calculating effect sizes and examining the roles of moderator variables. This approach permits a more comprehensive analysis of the effects of contraceptive use on psychological well-being.

Hypotheses

Considering past research, hypotheses on the relationship between oral contraceptive use and psychological well-being will hinge on oral contraceptive dosage and ingredients and specific populations of women. Monophasic contraceptives will have the least adverse psychological effects followed by biphasic contraceptives with triphasic contraceptives being most harmful. In addition, newer combination oral contraceptives will be associated with more positive psychological effects while progesterone- or estrogen-only contraceptives will be associated with more negative psychological effects. Lastly, women with a predisposition to a mood disorder, PMDD, severe PMS symptoms, and women who smoke will be at higher risk for adverse psychological effects.

Method

Sample of Studies

Only published studies were included in the meta-analysis. Research articles were collected by searching PsycINFO and Medline using the search terms *contracept* and *(well-being, depress*, and mood)* in which “*” is a truncation character that institutes a search for any
word having the designated stem. Additional articles were located using the reference lists of research articles identified in PsycINFO, MedLine, and previous literature reviews. Research studies were included that listed psychological well-being or mood as a primary or secondary outcome. Only studies using human participants conducted since the year 2000 were included. Studies were excluded that are no longer available or are in a language other than English.

Coding the Studies

Studies were coded on the following variables: organization sponsoring the study, whether the study was externally funded, whether mood was the primary focus of the research, sample size, randomization, where participants were recruited, country where the study was conducted, demographics (SES, age, race), any shared medical history of participants, OC ingredients and dosage, length of study, categorical or dimensional study, what scales were used to assess the dependent variables, what kind of experiment, statistical analysis, p-value, control group, placebo, attrition rate, reasons for attrition, results, and limitations and strengths.

Statistical Analysis

Hedge’s $d$ was used to estimate the effect size of the relationship between oral contraceptive use and psychological well-being. A positive effect size resembled an improvement of psychological well-being with contraceptive use. Conversely, a negative effect size resembled an impairment of psychological well-being with contraceptive use. Standard deviations, means, and $t$-values were converted to $d$ using Rosenthal (1994) formulas. Hedges and Becker’s (1986) formulas were used for calculating weighted effect size, confidence intervals, and mean effect size comparisons. The equivalent Pearson’s $r$ was also calculated for mean effect sizes.
Results

Initial database searches located 64 studies with relevant titles and abstracts. Fifty-one of those studies were excluded due to lack of a control condition (n = 36), insufficient data to calculate effect size (n = 7), the study's measured assessed variables such as jealousy (n = 1) or personality (n = 2), the study assessed menstrual symptoms only (n = 2), or the study was unavailable (n = 3). The remaining 13 studies included a total sample of 2,483 women. Only one hypothesis could be tested through meta-analysis due to lack of available studies. No sub-analyses could be performed so the hypotheses that monophasic contraceptives and combination estrogen and progesterone contraceptives would have less adverse effects than biphasic, triphasic, and single hormone contraceptives could not be tested. In addition, the hypothesis that women with PMDD, severe PMS, a mood disorder, or women who smoke would be at higher risk for adverse psychological effects could not be tested. The hypothesis that oral contraceptives would generally have a small positive relationship with psychological well-being was tested.

Table 1 lists the sample sizes and calculated effect sizes for these studies.

For the hypothesis that oral contraceptive use would have a slight positive effect on psychological well-being, the mean effect size (d) of the 13 useable studies was 0.151 (r = 0.075), \( z = 5.288, p < .0001 \), supporting the hypothesis. The index of variance of effect sizes (Q) was 48.808, \( df = 12, p < .001 \), indicating a large degree of variance among the effect sizes of the studies. Among the 13 useable studies, three (Gringnell et al., 2013; Kulkarni, 2007; Oinonen & Mazmanian, 2001) were identified as outliers because, unlike other studies, they had negative effect sizes. When these outliers were removed, the mean effect size did not change to a meaningful degree, \( d = 0.183, r = 0.091, z = 6.189, p < .0001; Q = 29.733, df = 9, p < .001 \).
Table 1

**Effect Sizes of Studies Included in the Meta-Analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Effect Size (d)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham et al., 2003</td>
<td>72</td>
<td>0.230</td>
</tr>
<tr>
<td>Atkin et al., 2010</td>
<td>210</td>
<td>0.000</td>
</tr>
<tr>
<td>Freeman et al., 2001</td>
<td>82</td>
<td>0.314</td>
</tr>
<tr>
<td>Gringnell et al., 2013</td>
<td>34</td>
<td>-0.493</td>
</tr>
<tr>
<td>Halbreich et al., 2012</td>
<td>274</td>
<td>0.295</td>
</tr>
<tr>
<td>Kulkarni, 2007</td>
<td>58</td>
<td>-0.392</td>
</tr>
<tr>
<td>Natale &amp; Albertazzi, 2006</td>
<td>62</td>
<td>0.423</td>
</tr>
<tr>
<td>Oinonen &amp; Mazmanian, 2002</td>
<td>79</td>
<td>-0.130</td>
</tr>
<tr>
<td>Pearlstein et al., 2005</td>
<td>32</td>
<td>0.849</td>
</tr>
<tr>
<td>Segebladh et al., 2009</td>
<td>118</td>
<td>0.056</td>
</tr>
<tr>
<td>Svendal et al., 2012</td>
<td>498</td>
<td>0.165</td>
</tr>
<tr>
<td>Yonkers et al., 2005</td>
<td>449</td>
<td>0.358</td>
</tr>
<tr>
<td>Young et al., 2007</td>
<td>515</td>
<td>0.000</td>
</tr>
</tbody>
</table>

\(^a\)A positive effect size indicates a positive effect of oral contraceptive use on women’s psychological well-being.

**Discussion**

Because of the small number of useable studies, the hypotheses that monophasic and combination estrogen and progesterone oral contraceptives would have less adverse psychological effects than biphasic, triphasic, and single hormone oral contraceptives could not
be tested. Similarly, the hypothesis that women with a mood disorder, PMDD, severe PMS, or who smoke would be at higher risk for adverse psychological effects could not be tested. The results of the meta-analysis supported the hypothesis that oral contraceptive use would have a small positive relationship with psychological well-being. The mean effect size showed a small statistically significant positive effect of oral contraceptive use on women's psychological well-being. However, there was also statistically significant variance among the results of the studies; studies varied from large positive to large negative effect sizes. When the three studies with negative sizes were excluded from the calculation, the overall effect size did not change to a meaningful degree, so the presence of negative outliers did not account for the small mean effect size. However, the effects of possible moderator effects could be a reason for the variance in effect sizes.

One such possible moderator is the health status of the women who participated in different studies. For example, Freeman et al. (2001), Halbreich et al. (2012), Pearlstein, Bachmann, Zacur, and Yonkers (2005), and Yonkers et al. (2005) included samples of women suffering from PMDD and had slightly larger positive effect sizes than studies including other samples of women ($d = 0.314$, $d = 0.295$, $d = 0.849$, $d = 0.358$, respectively). Gingnell et al. (2013) found the largest negative effect size at -0.493 and included women who had previously discontinued oral contraception due to adverse mood effects. Young et al. (2007), whose sample consisted of women diagnosed with non-psychotic major depressive disorder, found a near zero effect size. However, the small number of studies in each category precluded a statistical analysis of these differences.

The results of research of the relation between OC use and mood might also be affected by women's prior experience with contraception or their medical histories. For example,
Gingnell et al.'s (2013) results indicated that certain subgroups of women may be predisposed to adverse mood reactions from oral contraceptive use. Gingell et al. found that women with who had previously discontinued OC use due to adverse reactions were likely to experience adverse mood reactions again upon resuming usage. Based on fMRI imagery, the researchers found that left insula reactivity increased in women using OC, which may be indicative of depressed mood and increased anxiety. However, these women's adverse mood reactions could also be due to their anticipation of adverse reactions. In addition, Oinonen and Mazmanian (2001) found that there might be an interaction between mood stability during OC use and women's medical/family history. However, these were weak interactions and the findings were exploratory. Therefore, no firm conclusions can be drawn from the results of this study.

Another possible moderator variable could be type of OC that women use. However, my meta-analysis did not permit examination of this possibility because the useable studies examined only combined oral contraceptives. Young et al. (2007) did examine the effects of a progesterone-only contraceptive, but that study did not have a placebo or appropriate contraception use comparison condition so it was not possible to evaluate the effects of different types of OC.

Finally, the formulation of different combinations OCs in terms of the combinations of hormones included in them could act as a moderator variable. There was too much variability of hormone combinations among studies to do sub-analysis on this possibility. However, drospirenone and levonorgestrel, two common synthetic progesterone hormones, may have differing effects on psychological well-being. Several groups of researchers (Abraham, Luscombe, & Soo, 2003; Akin, Ege, Aksullu, Demiroren, & Erdem 2010; Gingnell et al, 2013; Halbreich et al., 2012) included contraceptives made with levonorgestrel and found effect sizes
that ranged from -0.493 to 0.295. Freeman et al. (2001), Pearlstein et al. (2005), and Yonkers et al. (2005) included contraceptives using drospirenone and had effect sizes that ranged from 0.314 to 0.849. Although the studies including drospirenone had larger positive effect sizes, these studies also included women suffering from PMDD. Therefore the larger positive effect size could be due to either variable.

Limitations

This meta-analysis had a various limitations. First, my meta-analysis had a very small sample of useable studies, which affects the generalizability of results. In addition, the useable studies were too different in regards to conditions included and too few in number to do further sub-analysis investigating the effects of possible moderator variables. Third, this study had only one researcher collecting and coding studies, could have led to bias because there was not way to evaluate the reliability of the codings. Finally, the terms used to search databases may not have been all-inclusive so that some potentially useable studies could have been overlooked.

Conclusions

My meta-analysis was unable to draw any firm conclusions about a relationship between oral contraceptive use and psychological well-being. There was a significant small positive relationship, but the significant large variance means the small positive relationship is not consistent. The large number of studies that had to be excluded, especially for a lack of a controlled condition or poor methodology, was concerning. There were too few studies and many studies were too poorly designed to provide much understanding of what happens to women’s psychological well-being when they use oral contraceptives. Future contraceptive research should always use a control condition and collect data both daily and at intervals of treatment in order to better understand the effects of oral contraception.
References

Note: Studies included in the meta-analysis are indicated by asterisks.


