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REVIEW

Hormonal Contraceptive Use and Affective Disorders: An Updated Review

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Video abstract

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Abstract: Hormonal contraceptives have given women historic freedoms and control over their fertility. At the same time, the potential side effects and unintended consequences of hormonal contraceptive use remain unclear due to a severe lack of funding and research. In this review, we summarize what is currently known about the impact of hormonal contraceptive use on mood symptoms, depression, and premenstrual disorders, and propose using the Social Signal Transduction Theory of Depression as a framework to generate predictions about the mechanistic pathways through which contraceptive use is associated with depression risk. The highest-quality evidence suggests that some types of contraceptives increase depression risk for some women. However, some contraceptives also appear to decrease depression risk in some instances. Key risk factors that predict depression following hormonal contraceptive use include age/age at onset of contraceptive use and mental health history/susceptibility. Hormonal contraceptives differ in ways that influence mood-related outcomes and can be used to treat depression in some women, especially those whose depression symptoms fluctuate across the cycle, indicating the potential presence of a premenstrual disorder. Looking forward, research, and funding for this research, is needed to elucidate the mechanistic pathways through which the use of different contraceptives impacts mood in different women to allow for a precision medicine approach to contraceptive treatment. In the meantime, health care providers should adopt patient-centered, "mindful prescribing" approaches to contraceptive counseling.

Keywords: women's health, hormonal contraception, depression, affective disorders, premenstrual disorders, mechanisms

Hormonal Contraceptive Use and Affective Disorders: An Updated Review

The FDA approved the first hormonal contraceptive (HC) method in 1960,[1,2] empowering women by giving them unprecedented bodily autonomy and freedom. HCs have enabled women to reduce unplanned pregnancies, increase time between successive pregnancies, and consequently engage in educational and economically productive activities—resulting in significant social mobility.[3,4] Indeed, modern women confidently pursue long-term investments in their careers that would have been unthinkable by their mothers and are now more likely than men to graduate with a bachelor's degree.[5]

Today, HCs are the most common method of contraception used by women in industrialized countries,[6] with 82% of women in the US reporting having used HCs for at least some period of their lives.[7] There are at least 200 different methods of HCs currently available, which are used by more than 300 million women worldwide.[8] HCs are safe and effective and provide various health-related benefits, including decreased risk of ovarian, endometrial, and colorectal cancers, less painful bleeding episodes, and enhanced bone health.[9–13] However, their use is not without side effects. Although adverse symptoms vary by individual and method, women most commonly report weight gain, acne, decreased sexual desire, bleeding changes, physical discomfort, and changes in mood when using HCs.[14,15]

Despite women citing mood-related side effects as a key reason they discontinue HC use[16] or are reluctant to begin HC use,[17] researchers often fail to find evidence of such side effects,[18,19] and research investigating the impact of HC use on mood and mood-related disorders has produced mixed results.[20–25] However, as more researchers have begun studying the unintended consequences of HC use, increasing evidence has emerged that suggests that at least some

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types of HC use are associated with increased depression risk in at least some women.[23,25] Given the ubiquity of HC use, it is vital to understand how HC use is associated with mood and mood-related disorders, who is at the greatest risk of experiencing negative HC-related mood changes, and who is most likely to experience positive HC-related mood changes.

Many past reviews have sought to determine if effects of HC use on mood and mood-related disorders occur (eg, refs[18,19,26–32]); therefore, in this review, we instead focus on potential theoretical and mechanistic explanations that can help to make sense of the mixed results obtained by past researchers investigating this topic. First, we provide an overview of what HCs are and how they work. Second, we briefly review affective disorders, with a focus on the Social Signal Transduction Theory of Depression. Third, we discuss the barriers preventing a straightforward understanding of the ways in which HC use is associated with mood and affective disorders before we critically review the mixed literature on associations between HC use and affective disorders, with a focus on research conducted between 2014 and 2024. Although our primary focus is on research conducted on HC use and affective disorders, we also review a few studies focused primarily on associations between HC use and mood, suicidal thoughts and behaviors, and premenstrual disorders (PMDs). Finally, we highlight the most promising and testable potential mechanisms which should be investigated to fill empirical gaps in this research area and suggest recommendations for clinicians who provide contraceptive counseling to patients. Together, we hope that addressing these topics will spur new research ideas and highlight key clinical issues involving HC use and mood disorders.

Hormonal Contraceptives

All contraceptive methods function to prevent pregnancy. Barrier methods (eg, condoms) prevent pregnancy by physically blocking sperm from entering the cervix, whereas hormonal methods prevent pregnancy by delivering synthetic hormones designed to prevent ovulation or implantation from occurring. HCs come in many forms, including a daily pill, implant, hormonal intrauterine device (IUD), quarterly shot, and weekly patch. All HCs contain progestins, synthetic versions of progesterone, and some also contain estradiol. Although some HC methods, such as hormonal IUDs, are thought to only contain "localized" hormones, this is a mischaracterization of how hormones act in the body; rather than being localized, any hormones that are delivered are instead carried throughout the bloodstream, binding to and interacting with receptors throughout the brain and body.[33,34] Although the dosage of hormones released each day in implantable devices is much lower than what is contained in oral pills, metabolic processes occurring during digestion of oral pills may limit the dosage of synthetic hormones which end up in the bloodstream, and metabolic rates for different progestins are poorly characterized.[33] As such, comparisons between dosages of implantable and oral pills should be made with caution. Additionally, progestins contained in HCs do not mimic the binding affinities of progesterone, varying substantially in their affinity to bind with and effect progesterone, androgen, glucocorticoid, and mineralocorticoid receptors (see Figure 1). Endogenous estradiol and progesterone levels are associated with many psychological and behavioral processes, influencing sexual desire,[35] inflammation,[36,37] reward reactivity,[38] eating behaviors,[39–41] and mood.[42] As HC use alters these hormone levels and their signaling pathways, it is unsurprising that HC use has side effects that impact numerous biopsychosocial processes, including emotional memory,[43–45] libido,[46–48] stress reactivity,[49–55] and mood.[56]

Affective Disorders

Affective disorders are those that impact mood, including major depressive disorder (MDD, also referred to as unipolar depression), bipolar depression (also referred to as bipolar disorder), seasonal affective disorder (SAD), and premenstrual dysphoric disorder (PMDD). Of these disorders, MDD—characterized by anhedonia, negative thought patterns, suicidal thoughts, disturbances in energy, concentration, appetite, sleep, and psychomotor function—is the most common, affecting approximately 17% of all men and 25% of all women during their lifetime.[57] Additionally, rates of depression appear to be on the rise, with 42% of high school students saying they felt sad or hopeless almost every day for at least two weeks in 2021, with significant increases occurring over the past 10 years.[58] At least 10% said they attempted suicide at least once that year.[58]

Critically, the lifetime burden of depression is not borne equally between men and women, as women are twice as likely to experience the disorder compared to men following the pubertal transition and lasting through menopause.[59,60]

Generation	1st	2nd	3rd	4th
Progestins	• Norethindrone/ Norethisterone acetate • Medroxy-progesterone acetate • Ethynodiol acetate	• Levonorgestrel • Norgestrel	• Desogestrel • Etonogestrel • Gestodene • Norgestimate	• Drospirenone • Dienogest
Progestational Effects	Moderate-high	High	High	Low
Androgenic Effects	Mixed (Low-High)	High	Low	Anti-androgenic
Glucocorticoid Effects	Moderate	None	Low	None
Mineralocorticoid Effects	None	Low Anti-mineraloc.	Mixed (High; None)	Mixed (High; None)
Modes of Administration				

Figure 1 Hormonal contraceptive types. Hormonal contraceptives (HCs) can be classified based on their generation of progestin, binding affinities, and mode of administration.

The fact that women's risk is increased specifically during hormonal transitions highlights that hormonal mechanisms are likely implicated.[61] Many treatments for depression have been developed, the most common of which are psychotherapeutic treatments, such as cognitive behavior therapy (CBT), and psychopharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs). Although psychopharmacological treatments are more accessible than therapy for many, only about 30–35% of adults achieve remission with current treatment approaches, leaving the majority of the disease burden of depression intact.[62,63]

One barrier preventing more effective treatment approaches for depression from being discovered and employed is the lack of a clear theoretical framework explaining how and why MDD develops, although effective therapeutic modalities can highlight potential mechanisms that influence MDD etiology. The serotonin or chemical imbalance theories of depression that prompted the medicalization of depression treatment have spurred decades of neuroscience research. Although a topic of some debate,[64,65] the success of SSRIs in treating depression in some suggests that serotonergic processes are associated with the disorder. Likewise, the success of CBT at reducing symptom severity in many suggests that cognitive mechanisms also contribute to the pathogenesis of MDD. Evolutionary models of depression suggesting that depression serves as a costly, hard-to-fake cue to social conspecifics that an individual needs help, support, or has unmet needs are plausible.[66] However, unlike other leading approaches, evolutionary theories of depression do not identify specific biological or psychological mechanisms through which depression develops and can be prevented or treated, focusing on behavioral and social mechanisms of action. The Social Signal Transduction Theory of Depression addresses these issues by describing the full set of neural, physiologic, molecular, and genomic

mechanisms that link experiences of social-environmental stress with internal biological processes that drive depression pathogenesis.[61,67]

Central to the Social Signal Transduction Theory of Depression is the fact that major life stressors are strongly associated with the onset of depression, often through inflammatory signaling pathways, and especially when stressors involve social threat. Although women are approximately equally likely to experience most major life stressors as a whole, they are much more likely to experience the specific types of stressors that most strongly predict depressive episodes (eg, interpersonal loss, social rejection), especially during the developmentally critical period of adolescence, when many women have their first lifetime episode of the disorder,[61] and when many women first begin HC use. Sex steroid hormones, but especially estradiol, influence depression risk by heightening threat perception, blunting cortisol reactivity to stressors, upregulating inflammatory processes, and modulating regulation of gene expression in ways that are highly context-specific. Using this theoretical framework, one could predict that HC use may increase women's depression risk specifically by altering sex steroid hormone levels in ways that result in increased threat perception, blunted stress reactivity, elevated inflammation levels, and altered transcriptional protein production.

Consistent with these predictions, researchers have found that HC use increases vigilance to negative emotional stimuli, implicating amygdala functioning,[45,55] which may increase threat perception in HC users. Likewise, HC use has a profound effect on women's cortisol levels, diurnal cortisol rhythms, cortisol and inflammatory reactivity to acute stressors, and chronic inflammation levels.[49–55] Further, emerging research suggests HC use results in altered gene expression in stress-related genes.[68] By using the Social Signal Transduction Theory of Depression to guide our understanding of how, why, when, and in whom HC use may impact depression risk, we can begin to test and unravel the potential mechanisms through which HC use influences the development and severity of affective disorders, make sense of conflicting results from past studies, and move towards a precision medicine approach to HC treatment.

Methodological Hurdles: Ethics, Causation, Biases, and Heterogeneity

As mentioned, past researchers investigating associations between HC use and depression have produced mixed results (see Table 1). When determining how to best weigh evidence across studies, it is important to consider the methodological decisions and obstacles inherent to conducting research on the unintended consequences of HCs. Although not insurmountable, there are ethical concerns with conducting prospective, double-blind, placebo-controlled, randomized clinical trials (RCTs), as women risk becoming unintentionally pregnant, which leads many researchers to use alternative designs instead—most commonly quasi-experimental designs. One option is to use another type of HC in place of a placebo, which would allow for comparisons between HCs with different progestins, dosages, and modes of administration. When high-quality study designs are employed, they tend to be within a specific clinical subset of women (eg, women with PMDs[69]). Although placebo-controlled trials are rare, placebo effects have been observed, and it has been suggested that nocebo effects also occur.[70] Critically, the length of treatment and follow-up in the highest quality studies tends to be short: depending on the mechanisms that drive effects, the impact of HC use on depression might take anywhere from 3-24 months[23] to emerge, however, most highly controlled studies conclude within 3–6 months of treatment.[26] The optimal timeframe of assessment has yet to be determined, as researchers have yet to assess women for longer than six months post HC-onset in a well-controlled study.

In quasi-experimental designs, researchers often compare participants using HCs to those not using HCs (ie, naturally cycling women); however, it then becomes difficult to discern if effects are caused by HC use or by other factors which cause women to decide to use or not use HCs in the first place. This issue, referred to as self-selection or common causes, is often the logic used by researchers who report no effects of HC use on outcomes after controlling for variables which may account for associations between HC use and depression. These variables often include smoking behavior, sexual activity, early age at sexual debut, and number of sexual partners. Another approach researchers have taken within these quasi-experimental designs is to compare women's mood-related processes between active pill days and non-active pill days among existing OC users (eg, refs[71,72]). Although an interesting way to glean insight into the active effects of HCs, separate out acute effects of hormone administration from organizational effects of continued HC use, and remove concerns about self-selection biases by focusing on within-person effects, it is important to keep in mind that the continuous alterations of sex steroid hormone levels (ie, the continuous intake of exogenous hormones which function by

suppressing endogenous sex steroid hormone levels) likely have organizational effects which also interact with the acute effects of pill administration (eg, ref[20]).

Another issue that impacts the interpretation of results from quasi-experimental designs is survivorship bias or the healthy user effect. That is, any sample of HC users taken from the population is going to be biased, overrepresenting women with the least/least severe HC-related side effects and underrepresenting those who experience the most/most severe HC-related side effects, since those with adverse side effects are unlikely to continue using the HC method which caused intolerable side effects. Finally, because heterogeneity in responses to HC treatment is now well documented (and expected by researchers concerned with self-selection or survivorship biases), caution should be used when interpreting only mean effects of HC use on any outcomes without exploring individual differences in users. If some women experience a positive effect, and others a negative effect, of HC treatment, the mean effect of HC treatment will present as having no effect. Although the study population in such a situation may have experienced no effect, on average, the individual women at the tails of the distribution certainly experienced effects.[73] Identifying factors that cause women to experience heterogeneous responses to HC treatment should be a primary goal of any researchers exploring the unintended consequences of HC use.

Heterogeneity of HCs

HCs come in different compounds (eg, progestin only vs combined pills), modes of administration (eg, daily pill vs quarterly shot vs IUD), dosages (eg, 0.125mg vs 1mg), and contain different progestins (eg, levonorgestrel vs drospirenone). As mentioned above, different progestins have differential binding affinity in the body – not only with progesterone receptors but also with androgen receptors, mineralocorticoid receptors, and glucocorticoid receptors (see Figure 1).

Although researchers often suggest that different types of HCs may have differential effects on women's mood and depression risk, a lack of knowledge about women's biology, or the mechanism of action of HCs on depression, makes it difficult to pinpoint which HC-specific factors deserve the most investigative attention. Possibilities include the mode of administration, if the method contains an estradiol component, the progestin, and the dosage.[73] One emerging perspective is that the androgenicity of progestins is a key factor that drives differences in women's responses to HC use.[18,27,51] Additionally, some researchers have found differences in cortisol reactivity to stressors between women using OCs and non-oral HCs that contain the same progestin at a different dose (eg, levonorgestrel[25]). This could indicate that the dosage or mode of administration is critical here; however, some caveats of IUDs should be mentioned. Although women using OCs do not ovulate, many women using IUDs resume ovulation within one year of IUD use,[74] indicating that the hormones released by the IUD may not entirely inhibit the cyclical hormone fluctuations of IUD users in the same way that an OC does. These differences in HCs, coupled with the fact that women taking many different types of HCs were nearly always grouped together in analyses in older research studies, makes HC-specific effects and their mechanisms difficult to disentangle.

Heterogeneity of HC Users

There are numerous individual differences and contextual factors that vary between women and situations, which have been shown to influence responses to HC use. The best-studied factors are age, age at onset of HC use, and duration of HC use. These factors are highly inter-correlated, making it difficult to disentangle their effects. Generally speaking, though, research has found that younger/adolescent users and those who have used HCs for a short duration of time (ie, two months to two years) have the most elevated risks of depression following HC onset, compared to adult-onset users and long-term adult users.[23,25] Other studies have found that adolescent-onset users experience some of the most striking and lasting HC-related effects on brain structure and function,[45,75,76] although links between these changes in brain structure and functional connectivity and depression risk remain relatively unexplored.

Additionally, a women's mental health history, predispositions to mood-related disorders, current stress levels, and early-life stress experiences all influence her risk of depression in general, and also are likely to play a role in depression risk following HC onset.[51,61,73,77–79] Contextually, one's goals and priorities, life stage, and knowledge about HCs is also likely to influence how HC use impacts mood and depression risk. Likewise, it is possible that one's reason for using

Table 1 Literature Review. To conduct this literature review, we searched the keywords "hormonal contraceptives", "birth Control", "affective symptoms", "depression", "depressive symptoms", "PMDD", "PMDS", "PMS", and "mood disorders" in Google Scholar and pubMed, and included papers published between 2014–2024

(a) Review of literature assessing the impact of hormonal contraceptive use on depression and depressive symptoms, published 2014–2024.

Study	Study Design	Sample Type	Exclusions	Study Result	Study Type	Method Limitations	HC Types Assessed	Individual Differences Assessed	Outcomes assessed	Covariates	Mechanisms Suggested
Anderl et. al., 2022[104]	Data from prospective cohort study; HC use between 16–19 years used as a predictor for depression in early adulthood	N = 725; Women followed from adolescence to early adulthood	Individuals using sex steroids other than HCs at age 16 or 19; Missing data	Adolescent HC use associated with a small but robust increased risk for experiencing an episode of MDD	Correlational, Population	Assessed presence but not duration of HC use; Lumped HC types; Self-selection; Survivorship bias; No random assignment	OCPs	Age	CIDI (depression)	Age; Ethnicity; SES; History of MDD; BMI; Menstrual pain; Acne; Virginity; Smoking; Stress; Age at menarche; Sexual orientation; OC use at age 25; Depressive symptoms	Gonadal hormones have long-lasting impact on brain and behavior and OCs impact these hormones
Engman et. al., 2018[21]	RCT with HC or placebo for three treatment cycles; Outcomes measured during baseline and third treatment cycle	N = 35; Mean age = 24.9; Women who previously experienced OC-related negative affect	Family history of psychiatric disorders & venous thromboembolism; Use of HCs two months prior to study onset; Ongoing psychiatric disorders; Contraindications for MRI scanning; Pregnancy	Depressive symptoms increased in the HC users, but not among the NC group, (group differences non-significant)	RCT	Intervention period of insufficient length to assess impact on affective symptoms	COC (EE/ levonorgestrel)	N/A	Depressive symptoms; resting state functional connectivity; Hormone levels (estradiol and progesterone)	N/A	Regional connectivity influenced by exogenous sex hormones, which in turn, impact mood
Lundin et. al., 2023[105]	Nationwide register study; Participants followed until event or 7 years after study onset	N = 792,913; Ages 15–24; Women with and without ADHD diagnoses	Contraindications for HC; Cardiovascular disease; Redeemed prescription of ovulation-stimulating drugs; Systemic lupus	HC use has no influence on depression in women without ADHD, but women with ADHD have an increased risk of developing depression when using HCs	Correlational, Population	Self-selection; Survivorship bias; No random assignment	All	ADHD diagnosis	Depression diagnosis; Prescription of stimulant medication	Medical indication for HC use; Parental history of mental disorders; Education; Age	Core symptoms of ADHD contribute to inconsistent pill consumption, leading to worsened pill side effects for individuals with ADHD

Skovlund et al, 2016[25]	Nationwide prospective cohort study; Women followed until event or 14 years after study onset, from 2000–2013; RRs calculated for first use of anti-depressant and first diagnosis of depression at psychiatric hospital	Nationwide prospective cohort study (Denmark)	Depression diagnosis or antidepressant prescription before study onset	HC use associated with antidepressant use and first diagnosis of depression; Risks decrease as age increases; HC types associated with differential risks	Correlational, Population	Self-selection; No random assignment	All	Age	First depression diagnosis; Antidepressant use	Edu level; PCOS or endometriosis diagnosis; BMI; Smoking	Progestins may have a negative impact on mood
Newman, 2022[85]	Cross-sectional survey to assess correlations between HC use, substance use, and depression	N = 3,320; Mean age = 19.1; College students	Non-binary or male gender identification	HC users had lower depression scores than NC women	Correlational	Duration of HC use not included in analyses; Self-selection; Survivorship bias; No random assignment	All	Cannabis use; Alcohol use	PHQ-9 (depression)	N/A	Individuals that cannot tolerate HC discontinue use; Potential interaction between cannabis use and HC on depressive symptoms
Lundin et. al., 2017[56]	RCT with HC or placebo for three treatment cycles; Outcome measured daily during baseline and third treatment cycle	N = 178; Ages 18–35	BMI > 30; Contraindications for HC use; Family history Contraindications for HC use; Use of treatments that would compromise uptake or metabolism of the contraceptive; See paper for additional health-related exclusions	HC use correlated with significant premenstrual improvement in depression scores	RCT	Self-selection; Intervention period of insufficient length to assess impact on affective symptoms; Survivorship bias	COCs (estradiol and nomegestrol acetate)	Duration of use; Previous adverse hormonal contraceptive experience	DRSP scores measuring daily depression, anxiety, mood swings, irritability, and decreased interest in usual activities	N/A	Study potentially included greater proportion of women with previous negative experiences of COC, such that population may have confounded results

(*Continued*)

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Table 1 (Continued).

Johansson et. al., 2023[23]	Population-based cohort study; RR calculated for HC use including duration, and outcome measures	N = 264,557; Ages 37–71; Median age at initiating and discontinuing HC use 21 and 32 years, respectively	Medical indication for use (individuals with dysmenorrhoea, endometriosis, PCOS)	HC use increases depression risk, particularly during first 2 years of use; HC use during adolescence may increase risk of depression later in life	Correlational, Population	Lumped HC types, Self-selection, Survivorship bias; No random assignment	All	HC onset; Age; Sibling depression occurrence	First depression diagnosis; UK Biobank mental health questionnaire to assess depression	SES; Number of births; PCOS; Age at menarche; Age at sexual debut; Family history of MDD	Gonadal hormones have long-lasting impact on brain and behavior and HCs impact these hormones
Zettermark et. al., 2018[106]	Epidemiological study; Followed from first HC use at baseline until prescription or end of one year follow-up	N = 815,662; Ages 21–30 at baseline	Psychiatric diagnosis in previous four years; Prescription fill of a psychotropic drug in previous four years; Individuals who delivered a child at follow-up	HC use is associated with psychotropic drug use (anxiolytics, hypnotics, sedatives, anti-depressants) among adolescent girls	Correlational	Duration of HC use not included in analyses; Self-selection; Survivorship bias; No random assignment	All	Age; HC type	Psychotropic drug prescription (anxiolytics, hypnotics, sedatives, anti-depressants)	SES	Healthy user bias explains higher incidence of psychotropic drug use in adolescent girls
Lisofsky et. al., 2016[107]	Three months of HC use compared with NC group; Outcomes assessed at baseline and end of third cycle	N = 56; Ages 16–33	Use of HCs within six months prior to study; Previous pregnancy; Hormonal disorders; MRI incompatibility; History of psychiatric or neurological illness	HC use is correlated with a decrease in grey matter volume; Grey matter reductions in amygdala linked to mood alterations in HC users	Quasi-Experimental; Correlational	Lumped HC types; Self-selection; Study period of insufficient length to assess impact on affective symptoms; No random assignment	OCs (COC and progesterone-only)	Changes in outcomes from baseline	Hormone levels (estrogen and progesterone levels); Cognitive performance; MRI data (structural + functional connectivity); PANAS (affect)	Age	Special sensitivity of the amygdala to female gonadal hormones
Doornweerd et. al., 2022[131]	Data from population cohort study; Participants followed for 9 measurement waves over 11 years	Data from nationwide online assessment survey given to undergraduates	Missing data for HC use	HC use not associated with increase in depression in late adolescence compared with NC group	Correlational	Lumped HC types; Self-selection; No random assignment	All	Age of OC onset	RADS-2 (depressive symptoms)	Age at menarche; Childhood trauma; Neuroticism; SES	Reduction in hormonal fluctuation by OC has protective effects

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Gregory et. al., 2018[132]	Data from nationwide online assessment survey given to undergraduates	N = 349,697; Ages 18–34	N/A	HC use significantly increased probability of depression diagnosis	Correlational, Population	Duration of HC use not included in analyses; Lumped HC types; Self-selection; Survivorship bias; No random assignment	All	Age; Hormonal vs non-hormonal contraceptive use	Depression diagnosis	N/A	N/A
Masama et. al., 2022[78]	Current HC users and NC participants completed outcome measures; Outcomes compared between HC groups and different stages of menstrual cycle in NC group	N = 388; Ages 17–29	Individuals who did not specify HC type	HC users displayed significantly higher depressive scores compared to NC group	Correlational	Duration of HC use not included in analyses; Self-selection; Survivorship bias; No random assignment	All	Menstrual cycle phases	Self-reported anxiety and depression symptoms; Perceived stress; Cortisol; Inflammation	BMI	HPA activity is dysregulated in women taking HCs, altering the HPA axis negative feedback mechanism and culminating in hippocampal cell loss, which could contribute to mental health disturbances
Lundin et. al., 2022[22]	National registry study; Women followed until event or 7 years after study onset	N = 739,585; Ages 15–25	Prior antidepressant use; Psychiatric diagnosis; Contraindications for HC use	HC users had lower or no difference in depression risk compared to NC	Correlational, Population	Duration of HC use not included in analyses; Self selection; No random assignment	All	Type of user (users, non-users, never-users, former-users); Type of OC	Depression diagnosis; Antidepressant use	Highest attained edu level; Medical indication for HC; Parental origin; Family history of mental illness; BMI; Smoking history	Precocious sexual behavior and drug use leads to depression

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Table 1 (Continued).

de Wit et. al., 2020[133]	Three waves of data from prospective cohort study used; HC use and depressive symptoms assessed at ages 16, 19, 22, and 25	N = 1,010; Ages 16–25	Serious health or language problems; Pregnancy; Use of other sex steroids	HCs showed no association with depressive symptoms overall; Adolescent users reported significantly higher depressive symptoms than their NC counterparts, including more crying, hypersomnia, and more eating problems	Correlational, Population	Lumped HC types; Survivorship bias; Self selection; No random assignment	OCPs	HC onset; Age; Duration of use	Youth self-report (depression)	Ethnicity; SES	Sex hormones influence brain development
Albawardi et. al., 2022[134]	Community-based cross-sectional study; Online survey	N = 4,853; Ages 21–45	Depression; Combined use of non-hormonal and hormonal contraceptives	High prevalence of depression among HC users compared with NC group	Correlational	Lumped HC types; Self-selection; Duration of HC use not included in analyses; Survivorship bias; No random assignment	All	Duration of HC use; Depression severity	PHQ-9 (depression)	Age; Previous psychiatric disorders; Previous physical illness; Substance use history	Progestins may have a negative impact on mood
Anderl et. al., 202[20]	Cross-sectional study on data from national survey; Compared women who first used HCs in adolescence to first use in adulthood and to never users	N = 1,236; Ages 20–39	Missing data	Long term association between adolescent HC use and elevated depression risk in adulthood regardless of current HC use	Correlational, Population	Lumped HC types, Self-selection, Survivorship bias; No random assignment	All	Age of OC onset	CIDI (depression)	Age at menarche; Age at sexual debut; Edu; Marital status; BMI; Endometriosis; Ever use of hormonal medications; Smoking history; Sex of sexual partners	Gonadal hormones have long-lasting impact on brain and behavior and OCs impact these hormones

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Zethraeus et. al., 2017[108]	RCT with HC or placebo for three months of treatment; Outcomes assessed at baseline and end of third treatment cycle	N = 340; Ages 18–35; BMI 19–30; Regular menstrual cycle (25–33 days); Using non-hormonal contraceptive at the study start; Fluent in Swedish	Smoking; Contraindications for HC use (see paper); History of hormone-dependent cancer; Undiagnosed bleeding; Pregnancy; Sex steroid hormone use during 6 weeks prior to study	No effect of HC use on depressive symptoms	RCT	Intervention period of insufficient length to assess impact on affective symptoms	COCs (EE + levonorgestrel)	Testosterone levels (total and free)	PGWBI; BDI (depression)	N/A	Progestins may have a negative impact on mood
Sultan et. al., 2024[135]	Cross-sectional study	N = 326; Ages 15–49; Women using HCs from one week to one year and non-users included	Depression or family history of depression; Use of psychiatric drugs; Chronic physical illness	No overall difference in depression scores between HC and NC groups, though individual depressive symptoms were significantly higher in HC group, including sadness, reduced libido, feelings of pessimism and failure	Correlational	Duration of HC use not included in analyses; Self-selection; Survivorship bias; No random assignment	All	Duration of HC use	BDI survey to assess depression	Smoking; BMI; Past and family history of mental disorders	Precocious sexual behavior and drug use leads to depression
McKetta et. al., 2019[82]	Data from nationwide survey; HC use, including duration, associated with outcome measures	N = 4,765; Ages 13–18	Pregnancy	No association between ever using HCs and lifetime depressive disorder, nor current use of HCs and current depressive disorder	Correlational	Self-selection; No random assignment	OCPs	Sexual activity	Diagnostic interview to assess depression	Age; Smoking; Age at sexual debut; BMI; SES	Sex steroids influence neural structures

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Table 1 (Continued).

Cheslack-Postava et. al., 2015[83]	US national survey data used; cohort study	N = 1,171; Ages 20–39; Former users, former long-term users, and never users included	N/A	Non-significant trend, HC use associated with somewhat reduced odds of depressive diagnosis	Correlational, Population	Duration of HC use not included in analyses; Self-selection; Survivorship bias; No random assignment	OCPs (monophasic vs multiphasic)	OC type	Psychiatric diagnosis	Age; Number of male sex partners last year; Edu; Race/ethnicity; SES; Marital status; Number of live-birth pregnancies; Current or recent pregnancy	Protective effect of HC against various disorders due to stable hormone levels across cycle
Roberts et. al., 2017[24]	Secondary analysis of military medical insurance records; HC use and outcome measures analyzed in 12 months postpartum	N = 75,528; Postpartum women in US military medical system	N/A	Risk of antidepressant use and MDD diagnosis in post-partum period varies with type of HC used	Correlational	Self-selection; Survivorship bia; No random assignment	All	Type of HC	Depression diagnosis; Antidepressant use	SES; Length of HC use	N/A
Yusuf et. al., 2024[136]	Cross-sectional study conducted between two hospitals	N = 227; Ages 15–49; Married Somalian women	Common mental illness diagnoses; Pregnant women	Significant association between HC use and depression, especially among women with shorter durations of HC use	Correlational	Lumped HC types; Self-selection; Survivorship bias; No random assignment	All	Type of HC use; Duration of HC use; Occupation; Edu level; Income; Age	PHQ-9 (depression)	N/A	N/A

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Bengtsdotter et. al., 2018[106]	Supplementary analysis of an RCT; Women treated with either HC or placebo during three treatment cycles; Outcomes measured at baseline, two months, and final cycle	N = 202; Ages 18–35; Women with diagnosis for mood/ panic/eating disorder; BMI 17–30	Contraindications for HC use; Family history Contraindications for HC use; Use of treatments that would compromise uptake or metabolism of the contraceptive; See paper for additional health-related exclusions	Women with ongoing or previous mental health disorders or risky use of alcohol have significantly greater risk of HC-induced mood symptoms including anxiety, mood swings, and irritability, but not depression or decreased interest in usual activities	RCT	Intervention period of insufficient length to assess impact on affective symptoms	COCs (EE and nomegestrol acetate)	Alcohol use; Previous or ongoing mental health disorders	DRSP scores measuring daily depression, anxiety, mood swings, irritability, and decreased interest in usual activities	N/A	Women with ongoing or previous mood disorders particularly sensitive to estrogen and progesterone effects
(b) Review of literature assessing the impact of hormonal contraceptive use on depression and depressive symptoms, focused on premenstrual disorders (PMDs), published 2014–2024.											
Eisenlohr-Moul et. al., 2017[70]	RCT; HC (EE and DROS) or placebo for three months of treatment; Outcome tracked through all treatment cycles	N = 55; Ages 18–40; Prospectively confirmed women with PMD	N/A	Across all groups PMS symptoms declined significantly	RCT	Intervention period of insufficient length to assess impact on affective symptoms	DROS/EE	Daily symptoms	*DRSP* to assess daily emotional and physical symptoms	N/A	High placebo response indicates relevance of placebo mechanisms to psychopathology of PMDs
Yonkers et. al., 2017[137]	Secondary analysis of a cohort study with a nested RCT; Used effect sizes to compare outcome between cycle phases in four premenstrual windows	N = 490; Ages 21–35	DROS users; Major depressive episode; Eating disorder; psychotic disorder; Receiving pharmacotherapy for psychiatric disorder; Recreational drugs at least once weekly; Severe suicidal thoughts; Hypersensitive to study compound; Pregnant	HC slightly attenuates menstrual cycle symptom change	Correlational, RCT	Lumped HC types	All	N/A	*DRSP* to assess daily emotional and physical symptoms	N/A	N/A

(*Continued*)

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Table 1 (Continued).

Shehata et. al., 2020[69]	RCT; Fluoxetine and HC, just HC, or placebo for six months; Main outcome was improved PMS in final cycle after five cycles of treatment	N = 300; Ages 20–40; Women with severe PMS	Underlying psychiatric disease; BMI >35; Women seeking pregnancy	Combined use of fluoxetine and HC containing DROS is superior to HC use alone in severe PMS	RCT	None	Oral fluoxetine and HC containing DROS	N/A	*DRSP* to assess daily emotional and physical symptoms; Number of women with improved PMS in final cycle of treatment (after 5 cycles)	N/A	COC inhibits ovarian activity reducing the effect of circulating sex steroids on serotonin, while fluoxetine inhibits serotonin reuptake
Takeda et. al., 2015[139]	Treated with EE and DROS for six cycles; Outcomes assessed at baseline and after three and six cycles of treatment	N = 48; Ages 20–49; Women with dysmenorrhea and premenstrual symptoms of PMS/PMDD	N/A	EE + DROS treatment significantly improved the severity of premenstrual symptoms	Quasi-experimental	Self-selection, Survivorship bias; No random assignment	EE/DROS	Duration of treatment	Premenstrual symptoms (questionnaire)	N/A	Combined OC pills prevent ovulation and stabilize hormone levels attenuating symptoms

Abbreviations: HC, hormonal contraceptive; MDD, major depressive disorder; OCP, oral contraceptive pill; SES, socioeconomic status; BMI, body mass index; RCT, randomized controlled trial; EE, ethinyl estradiol; COC, combined oral contraceptive; ADHD, attention-deficit/hyperactivity disorder; NC, Naturally cycling; OC, oral contraceptive; RR, risk ratio; PHQ-9, Patient Health Questionnaire-9; DRSP, Daily Record of Severity of Problems; CIDI, Daily Record of Severity of Problems; UK, United Kingdom; Edu, education; N/A, not applicable; PCOS, polycystic ovary syndrome; MRI, magnetic resonance imaging; PANAS, Positive and Negative Affect Scale; RADS-2, Reynolds Adolescent Depression Scale, Version 2; HPA, hypothalamic-pituitary-adrenal; BDI, Beck's Depression Inventory; US, United States; PGWBI, The Psychological General Well-Being Index; PMD, premenstrual disorder; DROS, drospirenone; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

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HCs (eg, to prevent pregnancy vs to address a medical concern) may also have implications for the type of HC used, one's tolerance for HC-related side effects, and the side effects experienced.

Without a clear understanding of the mechanisms of action through which HC use could impact depression risk, it is difficult to know which factors related to differences in responses to HC use and depression risk play a causal role in these associations. For example, in Ethiopia, women with iron deficiencies were found to discontinue HC use due to side effects, which included mood-related side effects, at more than twice the rate of those without iron deficiencies.[80] Although it seems unlikely that iron deficiencies fully explain the association between HC use and depression, this type of effect demonstrates the possibility that poorly explored mechanisms may link HC use with depression. This issue becomes problematic when researchers fail to account for key individual difference factors in analyses, either by not assessing them or by treating them as covariates instead of moderator/mediators. Although these analyses are typically well intentioned, without diagramming clear causal predictions about the mechanisms through which HC use impacts depression (eg, using Directed Acyclic Graphs [DAGs]), models that include many covariates are likely to misrepresent the strengths of associations between HC use and depression and may also yield incorrect conclusions.[81]

Past Research: Hormonal Contraceptives and Affective Disorders

Past research on associations between HC use and affective disorders has produced mixed results (see Table 1a). Some researchers have concluded that HCs have no effect on depression.[82] Others have reported that HC use is protective against mental health problems, improves mood and depressive symptoms, and that HC use can be used as a treatment option for those with both depression and PMDD, often outperforming SSRIs.[69,83] Others still have claimed that HC use worsens mood and depressive symptoms, increases the risk of developing depression, and may even cause depression.[23,25] Although these positions seem at odds with each other, they may all be somewhat true insofar as it is likely that different types of HC use have positive, negative, and no effects on depression in different women, depending on the woman, her biological makeup, and the type(s) of HC used. In the next section, we critically review a few key HC use and depression studies conducted over the last ten years.

HC Use Is Unrelated to Depression – "No Effects"

Many studies have reported that HC use has no effect on depression, which here, we differentiate from those which claim more nuanced effects. Some of these studies are high quality and should not be dismissed out of hand; however, the absence of evidence should not be taken as evidence of absence when the body of evidence is small or comprised of low-quality studies. For example, multiple researchers have conducted meta-analyses on past studies investigating links between HC use and depression. Despite many acknowledged limitations to the research reviewed, researchers concluded that progestin-only contraceptives have no effect on depression[19] and HC use only influences depression for adolescent users.[26]

Other researchers have reported effects of HC use on depression, which became nonsignificant when covariates were included in the model. For example, McKetta and Keyes[82] investigated associations between OC use and depression in a sample of 4,765 girls, aged 13–18 years old, drawn from the National Comorbidity Survey-Adolescent Supplement, a nationally representative US cohort study. However, it should be noted that of these, only 671 had ever used OCs and that information about other methods of HC use was not collected, meaning some non-users may have been using non-oral HCs. In unadjusted models, odds ratios for depression were increased for OC users compared to non-users (1.86) and never-users (1.60). When adjusting for covariates, including age, smoking, body mass index, age at sexual debut, and socioeconomic status (SES), odds ratios became non-significant (1.00 and 1.10, respectively), with age at sexual debut having the largest effect on reducing the association between OC use and depression. The researchers stated that their results mean that sexual promiscuity and smoking explained the associations between OC use and depression in adolescents, but it seems unlikely that the causal pathway from OC use to depression is entirely explained by adolescent promiscuity and smoking. This analytical design/interpretation assumes that the factors assessed here are themselves notable risk factors for depression; however, another interpretation, guided by the Social Signal Transduction Theory of Depression, is that these factors are better conceptualized as proxies for harsh early-life conditions or early-life stressor exposure, given the age of the population at hand.

One assumption that is implied by McKetta and Keyes[82] is that the pharmacological effects of HCs are not associated with any changes in depression risk. Rather, it is common causes of both HC use and depression which are responsible for elevated depression risk in HC users. A more nuanced perspective is to consider the meaning behind effects that disappear when controlling for key factors. For example, the implications here could also be that OCs increase the risk for depression in sexually active adolescents, but not in those who are not sexually active (or in those who are using OCs for a medical purpose). This framing of effects is a key difference between studies which analyze variables as moderators or mediators instead of covariates.

In general, predicted or assumed causal associations should always be mapped using DAGs before determining if factors are best modeled as covariates, moderators, or mediators. Especially in secondary data analyses, how a researcher decides to model and interpret factors determines what they will discover. In the subsequent sections, we review other studies that reported similar results as were reported here,[82] although they are modeled and interpreted differently. We strongly recommend that key factors which influence the associations between HC use and depression be assessed as moderators or mediators in future research. Controlling for individual difference factors to understand the true effects of HC use on depression is often misguided in smaller samples but can be essential in large samples, especially in secondary data analysis. The key is careful consideration of the possible causal associations between variables modeled. Based on the current available evidence, it is difficult to entirely reject the possibility that, overall, HC use has no effect on depression. However, this appears to be due to women's heterogeneous responses to HC use, not an overall lack of effect of HC use on depression risk.

HC Use Improves Mood or Depression

Multiple researchers have documented positive effects of HC use on mood and depression,[84,85] although in more recent studies, positive claims are often more nuanced.[83] That is, positive effects have been documented for some women after a short duration of HC treatment or for a specific HC type. However, we are not aware of any RCTs that have used a high-quality design and found that first HC use is protective for depression in non-clinical samples.

In one study that compared HC users to non-users (N = 3,320), researchers found that HC users reported less depressive symptoms than non-users,[85] although they were also more likely to use cannabis and drink alcohol more frequently. This study had a few methodological limitations, including participant self-selection, survivorship bias, all HC types were lumped together, and no individual differences between women were considered. The lack of random assignment to conditions, or longitudinal assessments, prevents meaningful interpretation of these correlations. Two potential strengths of the study include that the effects were not controlled away by other variables and that by exploring associations between HC use and substance use, the researchers may have probed one mechanistic explanation for how HC use in combination with substance use could influence depression symptoms.

In another large, cohort-based study (N = 1,171), Cheslack-Postava and colleagues[83] examined associations between OC use and depression, anxiety, and panic disorders in American women aged 20–39 using the National Health and Nutrition Examination Survey (NHANES), a nationally representative, publicly available dataset. Although the authors found no effect of OC use in the past year on past-year depression, they did find that OC use was associated with reduced rates of panic disorders. Because trends for depression, anxiety, and panic disorders followed similar patterns, the authors suggested that OC use may be protective against mental health disorders.

Again here, however, caution is warranted. Analyzing trends, comparisons between OC users and never users indicate that those who have never used OCs have the lowest rates of mental health conditions, whereas past OC users have higher rates of mental health conditions than do existing users. This could indicate a few things. First, as suggested, OCs may be broadly protective in users, such that ceasing OC use results in the emergence of mental health disorders. Second, women with preexisting mental health conditions or mental health conditions worsened by OC use may be the most likely to discontinue OC use or switch to non-oral or non-hormonal options (survivorship bias). Third, it could be the case that OC use worsens mental health conditions and has lasting effects, causing those who have previously used OCs to develop mental health conditions. To better understand this latter possibility, some researchers suggest using a new user design approach,[23,86] where it is not assumed that OC effects are the same in new vs long-term users. In fact, all

three of the interpretations for the results reported by Cheslack-Postava and colleagues[83] could be true, for some women, and for some types of OC use.

Beyond their primary analysis, the researchers also explored differences between users of monophasic and multiphasic OCs, and found multiphasic pill use was associated with a trend toward higher rates of diagnosed depression and that monophasic pill use was associated with a trend toward higher rates of subthreshold depression, compared to all women not currently using OCs.[83] This finding could indicate that monophasic OCs, which stabilize hormonal fluctuations across the cycle, are protective against depression in OC users. If so, this could also indicate that a larger proportion of female depression may be better classified as PMDD than is currently documented. In fact, the most straightforward conclusion that one could draw from studies which argue for a beneficial or protective effect of HC use on mental health is that cyclical changes in women's sex steroid hormone levels cause (at least some women) to experience depression and that reducing this cyclical variation in sex steroid hormone levels by administering exogenous hormones (ie, HCs) results in reduced depression.

Premenstrual Disorders (PMDs)

Indeed, cycle-based shifts in women's sex steroid hormone levels are associated with symptoms of depression in some women. PMDD is an affective disorder in which women experience clinically marked distress during periods of hormonal fluctuations across the cycle and also presents as a more severe expression of premenstrual syndrome (PMS), resulting in a notably greater burden of disease. Symptoms include pronounced mood swings, irritability, fatigue, heightened anxiety or tension, decreased interest in usual activities, and other depressive characteristics, alongside of physical symptoms (breast tenderness, muscle pain, weight gain, bloating).[87,88] Although current prevalence rates for PMDD are estimated at 2–8% in women of reproductive age, this number is likely an underrepresentation, as the constellation of nonspecific ailments that define this disorder makes it difficult to diagnose, and its inclusion in the DSM-V is still relatively novel.[89,90] Prior to the introduction of this diagnostic category, women who experienced depression-like symptoms in a cyclical pattern, beginning in the luteal phase and remitting within a few days of menses onset, would have been indicated for severe PMS.[91]

The cause of PMDD seems to be a complex interplay of biological, psychosocial, and environmental factors. Current theory suggests that PMDD is a disorder of suboptimal sensitivity to neuroactive steroid hormones (NASs).[92] Normal cyclic variation in estrogen and progesterone over the menstrual cycle causes changes in GABA, serotonin, and opioid responses of the central nervous system.[89] Some evidence suggests that PMDD pathophysiology is rooted in impaired GABA receptor subunit responses to fluctuations of the NAS allopregnanolone. This impairment is hypothesized to result in poor physiologic stress responses and related affective symptoms, ultimately culminating in the experience of PMDD.[92] Others have found that individuals with PMDD have a disrupted serotonergic system that is unable to appropriately adjust to ovarian hormone depletion after ovulation,[93] implicating serotonin in the etiology of PMDD.

HCs Can Be Used to Treat Depression and Premenstrual Disorders

Among the highest-quality studies investigating the impact of HCs on depression are those that have investigated HCs as possible treatments for depression and PMDs, as these are more commonly conducted as RCTs with enhanced experimental control compared to studies conducted on non-clinical populations[94–97,137] (see Table 1b). Since many of these landmark studies were conducted prior to 2014, we will not extensively review them here. Treatment options for PMDD include SSRIs such as fluoxetine, paroxetine, and sertraline (typically taken intermittently with symptom-onset),[91] as well as specific OCs. Many researchers have found that OCs containing the progestin drospirenone and ethinyl estradiol[98]—and sometimes desogestrel, to a lesser extent[99]—can provide beneficial outcomes in women with PMDs.[28,32,138] However, effect sizes are often small and placebo responses are common,[70,100] indicating that the complex interplay of environmental and psychological factors in the psychopathology of PMDs may have resulted in symptom improvement for both control and treatment groups in past studies.[70,97] Variation in treatment response, symptom type, and severity among women diagnosed with PMDD indicate that there could be multiple sub-groups of women who experience PMDD.[87] Therefore, individuals experiencing PMDD may be heterogeneous with respect to symptom patterns and even etiology, indicating a need for further understanding and subsequently personalized approaches to the disorder. Likewise, some researchers

have suggested that some cases of PMDD may be better characterized as premenstrual exacerbation (PME) of subclinical disorders including depression,[87] such that subclinical levels of symptoms are intensified during periods of hormonal transitions.

Overall, the certainty of evidence is frequently low: strong effects are not observed for most treatment approaches, including HC treatment, SSRIs, and other forms of therapeutic approaches specific to the symptom burden of PMDs.[32] Some recent RCTs studying HC use as a treatment for PMDs have excluded vulnerable populations with underlying mood disorders or individuals with a history of mental afflictions (eg, ref.[69,137]), indicating that groups experiencing the highest symptom burden, potentially as a consequence of their PMD, are especially understudied. Therefore, although the first-line treatment approach of a 24/4 regimen of OCs containing drospirenone is effective and tolerable in many, alternative options for treating PMDs are limited and optimal treatment strategies are not yet available. Future research is needed to develop treatment options that accommodate the family planning goals, mood-related symptom management, and medical needs of women experiencing PMDs.

HC Use Worsens or Causes Depression

The strongest evidence that HC use may cause or worsen depression comes from population-based studies using health registry data. In one such landmark study, Skovlund and colleagues[25] analyzed the health records of over one million Danish women across 6.4 years and found that HC use increased the risk of both first-onset depression and first antidepressant use. Risks were highest for adolescent users and peaked around six months after first use. Additionally, these risks were higher for those using non-oral and progestin-only options compared to users of combined OCs.

In a follow-up study using similar methods, the researchers found that HC use also predicted increased rates of suicide and suicide attempts, again with adolescent users driving these effects. They also found that those using non-oral and progestin-only options had the highest risk of suicidal actions following HC onset.[101] This pattern was also seen in a very large Swedish cohort of 15–22-year-old women ($N = 216,702$), for whom the use of combined and progestin-only pills was associated with increased risk of suicide, highest in the first month of use, then declining with increased duration of use.[102]

Population-based studies like these using historical health records have a few strengths, including that they account for survivorship effects, often have more information on HC types (allowing researchers to analyze HC-specific effects), large sample sizes, and can leverage longitudinal data collected over a longer time frame than existing prospective RCTs. However, these studies do suffer from a lack of random assignment, making self-selection and common causes difficult to account for, and often, as data are not collected on key moderating factors known to influence HC-related side effects and depression, the data available are not ideal to answer the most important questions about the impact of HC use on depression. Indeed, some researchers have critiqued the data analytic approach and conclusions of Skovlund and colleagues' landmark paper,[25] suggesting that small increases in depression risks for HC users reported are explained by unassessed factors, such as confounding genetic and psychosocial risks for depression, and claims should be tempered due to these limitations.[103]

Despite a lack of prospective RCTs, more recent evidence has emerged suggesting a causal role of HC use in depression. Using large-scale observational data from the UK Biobank ($N = 264,557$), Johansson and colleagues[23] found that OC users had a greater risk of depression than never users, which was especially pronounced during the first two years of use and in those who began OC use in adolescence, even if they ceased use later in life. Although all HC types were grouped together in this analysis, because of the time period during which women were reporting HC use, women would have primarily been using combined OCs containing levonorgestrel. Additionally, the researchers used a sibling analysis of 7,354 sister pairs and found evidence that OC use had causal effects on developing depression. Although this may only be true for a subset of women who are driving these effects, this study represents the strongest current evidence that HC use causes depression in some women.[23] Although they represent some of the most compelling studies exploring associations between HC use and depression, none of the studies we reviewed in this section provided insight into the mechanistic pathways through which HC use impacted depression or suicidality.

HC Use Is Sometimes Related Depression – "It Depends"

Thus far, we have highlighted studies which made the boldest claims and contained methodological limitations; however, many of these researchers did report nuanced results, exploring effects between HC types[19,25,83] and ages of users or age at HC onset.[23,25,32,104] The most robust findings when considering the body of research as a whole seem to be that HC use is associated with depression, depending on these factors. For example, Roberts and Hansen[24] investigated how the use of different types of HCs impacted depression risk during the post-partum period in 75,528 women enrolled in the US military medical system. Controlling for demographic variables, they found increased depression risk in the year following delivery for those using an implant or ring containing etonogestrel, and a decreased risk for those using norethindrone-only pills and a levonorgestrel IUD, indicating that the type of HC used influenced the direction of the effect of HC use on post-partum depression. Effects were moderated by age, SES, and military service, such that effects were stronger in younger women, of lower SES, and with a history of military service.[24]

Another study using Swedish health registry data ($N = 792,913$) found that women with attention-deficit/hyperactivity disorder (ADHD) were three times more likely to be prescribed anti-depressants compared to women without ADHD.[105] Following OC onset (but not the onset of non-oral HCs), this risk increased, such that women using OCs with ADHD were five times more likely to be prescribed anti-depressants compared to women without ADHD.[105] These results could indicate that women with ADHD are one subgroup of women who may be driving associations between HC use and depression, especially as ADHD is believed to be underdiagnosed in women.

Overall, the best supported take-home message in this area of research is that HC use is sometimes related to depression risk, in some users, in some contexts, using some types of HCs. The gold-standard research design for determining the causal effect of HCs on depression would be to use a prospective, double-blind, placebo controlled, RCT with follow-up assessments for 1–2 years post-HC onset. It is clear that methodological decisions, such as inclusion/exclusion criteria, outcomes assessed, categorization of HC types, and follow-up timing, have a large impact on results. Once data are collected, analytical choices and interpretation of results can differ greatly between different approaches. The highest quality analytic approaches are those that consider individual differences between women as factors as opposed to covariates, analyze effects based on timing of HC onset, and consider differences between different types of HCs. These approaches are also the most fruitful for identifying potential mechanisms through which HC use could impact depression risk. Here, we will highlight two possible mechanistic pathways through which HC use could increase depression risk in some women.

HC Use May Decrease Mid-Cycle Positive Affect

The first possible mechanism involves HC-related reductions in positive affect. Although many investigating the impact of HCs on mood have focused on the impact of HCs on negative affect (eg, refs[21,44,45]), which, consistent with predictions drawn from the Social Signal Transduction Theory of Depression, could result in increased vigilance for negative emotional stimuli and increased threat perception, a few researchers have investigated how HC use impacts positive affect as well. Alterations in positive affect may be a common unintended consequence of HC use and help to explain subclinical changes in mood reported by women who discontinue HCs. For example, in a high-quality RCT, researchers prospectively tracked mood-related symptoms in 178 women who were randomly assigned to use an OC (1.5mg estradiol, 2.5mg nomegestrol acetate) or a placebo for three months.[56] They observed worsening of symptoms between menses and the premenstrual phase of women's cycles (days 5–21) and some improvements of symptoms during the premenstrual phase in OC users. The effects appeared to be driven by users who reported previous adverse hormonal contraceptive experiences, indicating that there is likely a sub-group of women who are experiencing these negative mood-related changes when using HCs, as has been suggested by others (eg, ref[106]). This study is unique in that it investigated effects at different cycle phases and did not focus on HCs' ability to ameliorate mood-related symptoms during the premenstrual phase, which composes about one week of women's cycles, but instead highlighted the negative impact of HCs on women's moods during the more than two weeks prior to this time.[56]

In another line of research, Lisofsky and colleagues[107] used a within-person design to compare changes in brain structure and functional connectivity before and after three months of OC use (93% used a combined pill; 50% second generation and 50% fourth generation progestins). They compared changes following OC onset ($n = 28$) to a control

group of naturally cycling women (n = 28) over the same time course and found that HC use predicted decreased grey matter volume in the amygdala and altered functional connectivity in this region, along with a decrease in positive affect in the OC users from baseline to the three-month follow-up. Although this study lacked prospective assignment to conditions, its results, when considered alongside supporting evidence,[21,56] highlight one way in which OC use may influence depression risk. Specifically, a decrease in positive affect outside the premenstrual phase in OC users may drive women's increased depression risk in those who experience mood-related changes following HC onset.

This explanation is supported by another high-quality, prospective placebo-controlled RCT, which found decreases in well-being, but no increases in depression, in OC (150μg levonorgestrel and 30μg ethinylestradiol) users.[108] In the absence of HC use, estrogen peaks mid-cycle in naturally cycling women, and is typically associated with more positive moods. If HC use causes a lack of mid-cycle positive affect by suppressing cyclical rises in estradiol across the cycle, this could explain why OCs which suppress ovulation have been found to have larger effects on depression risk compared to IUDs which contain the same progestin in some studies, and why effects would differ for women with PMDs compared to those without. Cycle phase-specific changes in positive affect may have been overlooked by past researchers, either because researchers averaged effects across all cycle phases or focused on changes in negative affect in the premenstrual phase.

HC Use Alters Stress Reactivity

The second possible mechanism we propose involves HC-related alterations in stress reactivity that increase depression risk. It is well-established HC use results in alterations to women's cortisol levels, diurnal cortisol rhythms, and cortisol reactivity to acute stressors.[49–55] Specifically, HC users have been found to have elevated cortisol levels, an exaggerated and extended morning cortisol peak, and a blunted cortisol response to acute stressors compared to non-users.[49–55] Cortisol also modifies the association between HC use and depression symptoms, with hypothalamus-pituitary-adrenal (HPA) axis and hippocampal patterns in HC users that mimic those observed in animals exposed to chronic stress.[68]

The Social Signal Transduction Theory of Depression[61,67] posits that experiencing social stressors plays a large role in the onset of depression through HPA axis and inflammatory mechanisms. Drawing from this theoretical perspective, the alterations in stress-related biological processes and reactivity observed in women using HCs may increase women's risk of depression by inhibiting their ability to cope, either biologically or psychologically, with the stressors they experience. Supporting this possibility, researchers have investigated differences in the inflammatory response to acute stressors between OC users and naturally cycling women and found that OC users had an altered inflammatory response to acute stressors, which was, in turn, associated with decreased positivity in mood following the stressor.[51] Others have found HC users to have elevated chronic inflammation,[78,109] which is itself a risk factor for depression.[110,111] Elevated inflammation in HC users may be caused, in part, by blunted cortisol reactivity to stressors,[51] as cortisol downregulates inflammatory stress responses. Therefore, alterations in stress- and inflammation-related processes represent supported, plausible, and testable mechanistic pathways through which HC use may influence the development and severity of affective disorders. The next steps here include discovering the mechanistic pathways through which HCs impact cortisol levels and signaling, identifying the HC types which have the strongest and weakest effects on these pathways, and more deeply investigating whether altered cortisol levels and reactivity are strongly associated with depression in HC users.

Considerations and Future Directions: Research & Prescribing Approaches

The lack of clarity as to associations between HC use and affective disorders stems from a few sources. As discussed above, HCs are not a homogenous group. Likewise, women have different responses to the same HCs, different vulnerabilities to affective disorders, and experience other contextual factors which may influence responses to HCs. Any study investigating the impact of HC use on depression which concludes with a strong claim, without caveats for the heterogeneity of mood-related responses to HC use, should be viewed skeptically.

Additionally, research on the impact of HCs in women has lacked sufficient funding support and, as a result, suffers from numerous critical methodological limitations (eg, small sample sizes, lack of randomization and appropriate control groups, little examination of potential moderating factors, limited follow-up time periods). Further, this research is often hampered by political and social implications of the possible results. As alluded to above, we also lack clear theoretical

and mechanistic understandings of depression and PMDs and thus how HC use impacts these outcomes. Research is thus sorely needed to fill these gaps. Looking forward, therefore, we encourage prescribers to engage in *mindful prescribing* of hormonal contraceptives, to maximize the benefits of hormonal contraceptive use while minimizing the potential risks.

Basic, Mechanistic Research on Females and Women's Health Is Needed

The biggest barrier to understanding effects of HCs on depression is the historic lack of women's health research and funding. Although the National Institutes of Health (NIH) now emphasizes the need to include women and female animals in clinical research, decades of health-related research has been conducted using only men and male animals. The present literature based on this topic is thus severely limited, making it extremely difficult to draw well-justified hypotheses about possible moderating factors and underlying mechanisms of HC use in women. Research into women's health has recently gained momentum; however, diseases that are female-dominated are, still today, significantly underfunded relative to their disease burden and compared to disorders that are male-dominated.[112,113] As a result, researchers know strikingly little about the life-altering health conditions that half of the world's population experience.

Relatedly, efforts within the NIH to advance women's health research have struggled to significantly move the needle. The Office of Research on Women's Health, for example, has no research budget and cannot award intramural or extramural grants to support studies on women's health. As such, all research proposals focused on women's health are reviewed by other study sections and must be tailored to fit an NIH institute's priority (eg, aging, cancer, mental health), as there is no NIH women's health institute. This fact has caused a dire lack of fundamental knowledge about basic female biology and health, since NIH institutes lack a primary congressional mandate to conduct studies on women's health or biology. Moreover, it could be argued that the current outcome or disorder-focused structure of NIH has resulted in a very siloed approach to studying women's health (and health in general) and has wasted significant resources, given that basic processes in female biology have, in turn, been simultaneously studied in numerous different contexts with no overall strategic plan.

Based on what we do know, the true associations between HC use and affective disorders are clearly nuanced. As evidence accumulates, so too does the need to discover the biological mechanisms that link HC use and affective disorders. Given decades of research that has failed to discover purely biological mechanisms underlying the etiology of depression, there are likely interacting biological, psychological, and social mechanisms driving the disorder.[61,67,114] At the same time, given high rates of depression in women between puberty and menopause, the onset of depression in many women cyclically and postnatally, and that HC use impacts depression risk in at least some women, it is likely that exploring hormonal influences on depression in women will be empirically fruitful. Investigating changes in depressive symptoms following HC onset using intensive longitudinal designs can act as probe into these mechanisms, which could in turn shine light not only onto the ways in which HC use impacts depression but also on female-specific mechanisms of depression pathogenesis and the specific individual differences which predict if women are likely to have positive, negative, or neutral responses to HC use.

Implications of Outcomes, Political Motives, and Societal Pushback

Due to their implications for women's fertility, HCs have been imbued with a particular social and political volatility, which can make funding research on their effects undesirable. Both scientific and anecdotal information relating to the consequences of HCs have been weaponized by political movements both seeking to hamper women's reproductive rights and those seeking to expand women's reproductive rights while also being misconstrued, exaggerated, and minimized by internet sources. Indeed, there is a prominent political and religious agenda in America which champions restricting access to reproductive options including in vitro fertilization (IVF), abortion, gender affirming care, and contraception. In a concurring opinion with the overturning of Roe v. Wade, Justice Clarence Thomas argued that the court "should reconsider" its past rulings codifying contraception access.[115] He was joined by other prominent figures who have argued against HC access, using exaggerated and decontextualized experiences to legitimize their claims.[116] On the other hand, those championing the case for women's reproductive freedoms benefit from a narrative that HC use is entirely safe and that neither women's cyclically changing hormones nor their HC use impacts their behaviors,

cognitions, or health. Neither societal force promotes the investigation of accurate, nuanced, and variable effects of HC use.

The tenuous political and social context surrounding HC use creates a contentious situation for funding at a time when research on HC use, and its potential side effects, is desperately needed. Our review of the current state of the literature linking HC use to depression, for example, has highlighted many serious limitations. Consequently, we know very little about how differences in HC methods and users can result in various side effects. Among improving scientific knowledge as to the impact of HC use on depression, high-quality studies which temper the reactionary claims about risks (and lack of risks) of HC use will enable medical professionals to take back control of the current discourse surrounding HC side effects. To maintain scientific integrity in this area, unbiased research funding must be available to those seeking to characterize the unintended consequences of HC use, and funders must remain neutral and unbiased when considering potential sociopolitical reception of research findings.

People are questioning HC use for a variety of reasons, including concerns about physical and mental health side effects.[16] Relatedly, many in Western countries have taken to the internet to share their dissatisfactory experiences with HCs, and their reasons for discontinuation. These testimonies are largely based on the fact that women feel as if their health care professionals do not inform them sufficiently, do not involve them in the decision-making process, and overlook their complaints as being misconceptions.[117] This is partially a consequence of an emerging culture of medical consumption, in which health consumers conduct their own research independent of medical experts, giving rise to a reconceptualization of individual empowerment as a result of interactions with online social environments.[118] Additionally, differences in perspectives between researchers investigating potential side effects of HC use in westernized countries and those doing similar work in developing countries, who are more focused on contraceptive uptake as a force for good, have emerged in recent years. Although the prevalent narrative in research emerging from developing countries is that HCs are safe and effective, and that side effects are benign or uncommon, this has much to do with very different contexts of use and costs and benefits for users. Instead of seeking to label or present all contraceptives as always positive or always negative, we should strive to achieve contraceptive autonomy,[119] in which users have the information they need to make informed decisions about the costs and benefits of different types of contraceptive use. For many potential HC users, this begins at a doctor's visit.

A Call for Mindful Prescribing

The challenges to effectively prescribing HCs are not unique and mirror many of the challenges faced in treating depression. In both cases, there are many options available, it is unlikely the doctor prescribing treatment is a specialist in the area, and it is difficult to discern which options are best for each individual person based on the current knowledge base. We recommend that a mindful prescribing approach is employed both by those prescribing HCs to patients and to those prescribing treatments for depression and PMDD as well (see Figure 2).

The first step to mindful prescribing involves conducting a careful risk assessment prior to making treatment recommendations, which can then be used to weigh the costs and benefits of different treatment options. After careful profiling of patient characteristics and risk factors (ie, pertinent psychiatric history, medical history, family history, experiences with past HC methods and reproductive events, patient values and goals, and current mental health), prescribers can discuss contraceptive options which minimize the potential of negative side effects while maximizing positive benefits with patients. Although this sounds like common sense, formal assessments of possible moderating factors that impact HC responses are rarely performed in clinical care, and there are numerous factors that could potentially interact with HC use and lead to unintended consequences.

One solution is to use contraceptive decision aid tools, which have been found to increase women's reproductive self-efficacy and knowledge and result in more positive contraceptive use intentions.[120–124] Although such tools will require additional research to optimize decision algorithms, what is key here is that tools like this highlight a pathway towards modernizing the way we prescribe and use HCs.

In the absence of a decision aid tool, even a cost-benefit discussion with a patient based on limited information can be useful. Prescribers can determine which side effects a potential user would find most intolerable, which potential benefits might outweigh potential costs, and involve women in the decision of which contraceptive option they select. By

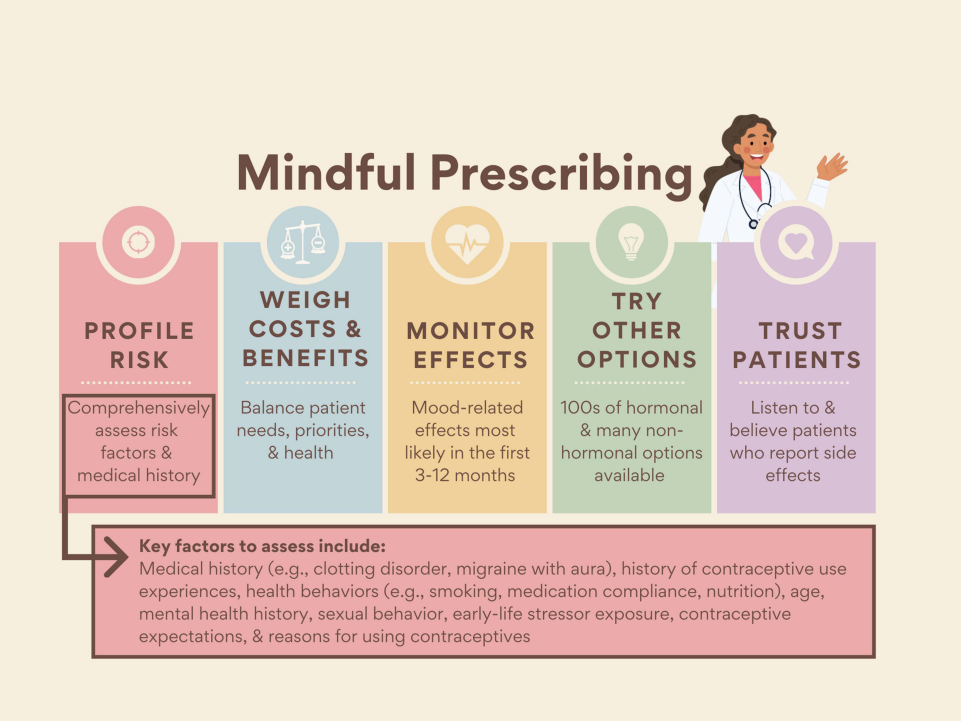

Figure 2 A Call for Mindful Prescribing. During contraceptive counseling, providers should practice mindful prescribing by conducting comprehensive risk assessments, which they use to discuss the potential costs and benefits of multiple different contraceptive options with each individual patient. If hormonal contraceptives are prescribed, effects should be monitored for 3–12 months, especially for those who are at a high risk for mood-related outcomes. If side effects emerge, providers should encourage women to try another contraceptive option, either with a different progestin or dosage, or a non-hormonal option, like a copper intrauterine device (IUD). To find the best contraceptive option for their patients, providers must also trust, listen to, and believe patients when they report possible contraceptive-related side effects.

discussing the possible costs and benefits of potential contraceptive options, users gain agency in their health care decisions and are more likely to reliably use their contraceptive method of choice, decreasing the risk of undesired pregnancy.[125,126] Although discussions between doctors and patients about modes of HC administration are common, discussions about different formulations of HCs are less so. Given that women respond differently to different types of HCs (eg, OCs which differ primarily in the androgenicity of their progestins), these nuanced choices need to be seriously considered when prescribing contraceptives.

Following a prescription to a HC, women should be closely monitored for mood-related changes for at least the first 3 months—but ideally through the first 24 months—of HC use. This is especially true for adolescents, given their increased risk of developing depression following the onset of HC use,[20,23,25,104] and others with a high risk for mood-related outcomes of HC use. Prescribers should also be open to changing treatment options for women who experience undesired consequences of HC use. There are hundreds of different contraceptive formulations available, and no one should feel that they have no choice but to suffer through their contraceptive. Often, this scenario arises because prescribers do not listen to, trust, and believe patients when they report side effects.[117] This is especially true for women, minorities, youth, those who lack reliable access to medical care, and anyone reporting mood-related side effects of a common medication.[127–129] Too often, women and girls who report such changes are dismissed by doctors. Even if the prescriber thinks the symptoms are "all in her head", they still may have a profound impact on a patient's mental health, physical health, and well-being.

Small steps to improve prescribing practices may have a large influence on women's experiences with HCs, as emerging evidence suggests that prescribing habits of physicians influence the likelihood that patients will both use HCs and develop depression. A recent preprint exploring prescribing patterns in a population study in Denmark reported that being assigned to a high-prescribing physician strongly predicts OC use by age 16 and leads to worse mental health outcomes from 16 to 18 years old.[130] With what we currently know, it is essential for health care providers to seriously consider the costs and benefits of HC use in their patients. To aid them in this effort, decision aid tools that facilitate

a precision medicine approach to HC treatment could reduce the burden on health care providers, helping providers to select the best contraceptive option for each woman while also reducing side effects of HC use in women – which could in turn reduce overall rates of depression in reproductive-aged individuals. Although research gaps still exist, we have learned a lot about the HC-related side effects different women experience when using different HCs in recent years, which is beginning to make possible a precision medicine approach to HC use.

Conclusion

In conclusion, HCs are widely used, and women deserve better information about the trade-offs they are making when they decide to use HCs. Likewise, health care providers deserve a better science base from which to make treatment recommendations. Research on female-specific mechanisms of depression and unintended consequences of HC use have been hampered by a historic lack of inclusion of females and female animals in clinical research. It is thus time to more seriously invest in research on women's health in a manner that matches the disease burden experienced by this population. Along these lines, we propose that using the Social Signal Transduction Theory of Depression as a framework to guide mechanistic explorations into associations between HC use and depression will be especially fruitful, helping researchers make better sense of mixed results, inform predictions, and clarify assumptions underlying different modeling approaches.

Today, we know that HCs have unintended consequences, which, for some women, in some contexts, using some HCs, include increased risk for depression. Although the unintended consequences of an undesired pregnancy far outweigh those of HC use, many hormonal and non-hormonal contraceptives are available, and these alternatives should be considered when women experience adverse mood-related symptoms following HC onset. Likewise, some HCs can also be effective in treating depression in some women, especially in the case of PMDs including PMDD. Not all contraceptive options are created equal, and we encourage providers to practice mindful prescribing by performing risk assessments and selecting contraceptive options that minimize the potential of negative side effects while maximizing positive benefits of contraceptive use. By adopting these clinical practices, and by mustering the social and political courage to support women's health research as is warranted, we will be investing not just in the wellbeing of our daughters, mothers, and grandmothers but in the livelihoods of all who are touched by the ability of women to live healthy, fulfilling lives.

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