BI-08 Hormonal contraception and its effects

For over six decades, the widespread availability of hormonal contraception (HC) has fundamentally altered the demographic, economic, and social trajectories of modern societies. By chemically uncoupling sexual intercourse from reproduction, it has facilitated vast shifts in education, workforce participation, and relationship dynamics. However, this profound cultural transformation is underpinned by an equally profound biological intervention: a large share of Western women have lived their adult lives under an altered endocrine state. Modern hormonal contraceptives—including combined oral contraceptives (COCs), progestin-only pills (POPs), transdermal patches, vaginal rings, and levonorgestrel-releasing intrauterine systems (LNG-IUS)—operate by overriding the endogenous hypothalamic-pituitary-gonadal (HPG) axis, suppressing natural hormonal fluctuations, and introducing continuous levels of synthetic steroid analogs.

To systematically evaluate the impact of this mass endocrine alteration on mood, stress, cognition, and mate choice, this foundational report stratifies the evidence into three distinct layers: the physiological layer (measurable biological and neurological changes), the behavioral layer (statistical shifts characterized by overlapping distributions), and the cultural layer (variable societal outcomes).

The Physiological Layer: Neurobiology and Endocrinology

The physiological layer encompasses the measurable, mechanistic alterations induced by exogenous hormones. Hormonal contraceptives are not biologically neutral; their synthetic estrogens (typically ethinyl estradiol, or EE2, and increasingly, natural equivalents like estradiol valerate or estetrol) and synthetic progestins cross the blood-brain barrier. There, they interact with widespread steroid receptors in neuroanatomical regions critical for emotion regulation, cognitive processing, and stress reactivity.

Structural and Functional Brain Architecture

Neuroimaging studies consistently demonstrate that HC use alters both the structure and the resting-state functional connectivity (rs-FC) of the human brain. The synthetic steroids in HCs bind to estrogen and progesterone receptors located densely in the hippocampus, amygdala, and prefrontal cortex. In a structural magnetic resonance imaging (MRI) analysis published in *Frontiers in Neuroscience*, Pletzer (2019) demonstrated that COC use is associated with altered gray matter volumes in the prefrontal cortex, anterior cingulate cortex (ACC), fusiform gyri, hippocampus, and basal ganglia[1]. These structural alterations have been replicated across multiple independent neuroimaging cohorts, establishing that exogenous hormones physically modify regions responsible for fear processing and emotional regulation[3].

Functionally, HC use modifies the brain's intrinsic network organization. Utilizing a Triple Network Model—comprising the Default Mode Network (DMN), Salience Network (SN), and Executive Control Network (ECN)—Pletzer et al. (2023) conducted a double-blind randomized,

placebo-controlled trial involving 34 women, published in *Translational Psychiatry*[5]. They demonstrated that during COC treatment, there is a distinct pattern of enhanced connectivity within the DMN and decreased connectivity within the ECN. Furthermore, the dorsal ACC (a core hub of the SN) mediates an increased recruitment of the DMN by the ECN during treatment. Crucially, these specific connectivity shifts correlated directly with adverse mood side effects; network connections related to increased mood lability showed significant hyper-connectivity exclusively during the COC treatment phase[5].

Further resting-state analyses indicate a loss of individual connectome idiosyncrasy among pill users. Studies utilizing dense-sampling functional connectome fingerprinting have revealed that synthetic hormones homogenize brain dynamics across users by restricting local spatiotemporal synchronization while altering global integration across neural scales[2]. This loss of neural idiosyncrasy has been statistically linked to increases in negative affect and depressive symptoms[6].

Amygdala reactivity is also profoundly affected by the pharmacological suppression of the HPG axis. In an fMRI study evaluating neural responses to emotionally arousing stimuli published in *Social Cognitive and Affective Neuroscience*, Pletzer et al. (2014) observed that women using COCs exhibited significantly decreased bilateral amygdala reactivity to negatively valenced stimuli compared to naturally cycling women[3]. Because the amygdala is critical for emotional memory and fear processing, this dampening effect represents a measurable neurobiological mechanism for "emotional blunting," a phenomenon frequently reported as a subjective side effect by long-term HC users[3]. This finding has been widely replicated, solidifying the consensus that oral contraceptives modulate central affective networks[3].

The Hypothalamic-Pituitary-Adrenal (HPA) Axis and Stress Reactivity

The interaction between HC use and the Hypothalamic-Pituitary-Adrenal (HPA) axis—the body's primary physiological stress response system—is one of the most robust physiological findings in the literature. Oral contraceptives undergo extensive hepatic first-pass metabolism. Exogenous estrogens stimulate the hepatic synthesis of multiple binding proteins, notably corticosteroid-binding globulin (CBG). By upregulating CBG, COCs bind a larger proportion of circulating cortisol, which paradoxically leads the adrenal glands to increase total cortisol production to maintain homeostasis[9]. Concurrently, the suppression of endogenous ovarian hormones (which normally exert inhibitory feedback on the HPA axis) removes a critical neuroendocrine brake[9]. (It is worth noting that newer formulations utilizing the fetal estrogen *estetrol* demonstrate significantly less hepatic stimulation of CBG compared to ethinyl estradiol, though long-term psychiatric data on estetrol remains in its infancy[11]).

Behaviorally and physiologically, this HPA dysregulation results in a blunted cortisol response to acute psychosocial stress. In standardized laboratory stress paradigms, such as the Trier Social Stress Test (TSST), naturally cycling women in the luteal phase typically mount a robust salivary cortisol response. In stark contrast, COC users consistently demonstrate a blunted or entirely absent cortisol response[13]. This finding has been replicated across dozens of independent studies and confirmed in systematic reviews, making it a highly reliable physiological marker of HC use[13].

Hertel et al. (2017) provided a critical genetic and molecular mechanism for these stress-like alterations in a study of 233 pre-menopausal women, published in *Scientific Reports*[10]. They found that OC use not only increased circulating total cortisol but also elevated the transcription of *FKBP5*, a glucocorticoid-regulated gene that acts as a co-chaperone inhibiting glucocorticoid receptor (GR) sensitivity[10]. By promoting GR resistance, OCs mimic the precise physiological profile of chronic psychological stress. Crucially, Hertel et al. found that these effects were moderated by the *FKBP5* rs1360780 genotype—a specific genetic polymorphism previously linked to an increased risk for stress-related psychiatric disorders, including major depression[10]. This indicates that the HPA-blunting effect of the pill interacts directly with an individual's underlying genetic architecture.

The Oxytocin System and Pair-Bonding Mechanisms

Endogenous oxytocin (OXT) plays a pivotal role in pair-bonding, social approach behavior, and reward processing in mammals. The physiological impact of HCs on this system offers a mechanistic explanation for reported shifts in relationship dynamics. Scheele et al. (2013, 2016), in studies published in the *Proceedings of the National Academy of Sciences (PNAS)*, demonstrated that in naturally cycling women, intranasal OXT administration increases the perceived attractiveness of a romantic partner relative to other men, a behavioral shift paralleled by elevated neural responses in the nucleus accumbens (NAcc) and ventral tegmental area (VTA)[18].

However, in women using hormonal contraceptives, this oxytocin-mediated reward response is virtually abolished[18]. Because gonadal steroids are essential for regulating the density of oxytocin receptors and baseline OXT production, the synthetic suppression of the HPG axis appears to antagonize the partner-specific modulatory effects of OXT. While oxytocin's pair-bonding effects have been flawlessly replicated in animal models (e.g., prairie voles), human behavioral paradigms are notoriously noisy. Nonetheless, the physiological disruption of the neurochemical pathways underlying romantic attachment provides a plausible biological basis for behavioral shifts in sexual and emotional intimacy among HC users[20].

The Behavioral Layer: Overlapping Distributions and Statistical Shifts

The behavioral layer translates the aforementioned physiological mechanisms into observable psychological phenomena: mood fluctuations, clinical depression, cognitive biases, and sexual behavior. A critical requirement for analyzing this layer is distinguishing between averages and individuals. Because behavior is highly multifactorial, the effects of HC manifest as statistical shifts in overlapping population distributions. What is observed as a small or statistically null average change at the population level can represent severe, life-altering clinical consequences in the tails of the distribution.

Depression and Suicidality: Registry Studies vs. Randomized Trials

The debate over whether hormonal contraceptives cause depression is perhaps the most heavily contested topic in modern women's health. The evidence base is split between massive, population-wide observational registry studies (which are statistically powered to detect rare

events but suffer from inherent confounding) and smaller randomized controlled trials (RCTs) (which establish absolute causality but frequently lack the statistical power to capture rare but severe adverse psychiatric effects).

The Danish and UK Registry Evidence

The most compelling epidemiological evidence originates from a landmark Danish registry study by Skovlund et al. (2016), published in *JAMA Psychiatry*. Analyzing a cohort of 1,061,997 women (ages 15-34) with no prior history of depression, the researchers found that HC use was significantly and causally associated with a subsequent first diagnosis of depression and the first use of antidepressants[22].

The risk varied significantly by the pharmacological formulation and delivery method. The relative risks (RR) of first antidepressant use compared to non-users are detailed below:

Contraceptive Method	Relative Risk (RR)	95% Confidence Interval
Combined Oral Contraceptives (COC)	1.23	1.22 - 1.25
Progestin-Only Pills (POP)	1.34	1.27 - 1.40
Levonorgestrel IUS (LNG-IUS)	1.40	1.31 - 1.42
Vaginal Ring	1.60	1.55 - 1.69

Data sourced from Skovlund et al., 2016, JAMA Psychiatry[22].

The psychological vulnerability was most acute among adolescents (ages 15-19). In this critical neurodevelopmental cohort, the RR for combined pills rose to 1.8, and for progestin-only pills, it spiked to 2.2[22].

In a chilling subsequent study on suicidality (Skovlund et al., 2018, *American Journal of Psychiatry*), examining 475,802 women over an average follow-up of 8.3 years, the researchers utilized propensity score matching and identified 6,999 suicide attempts and 71 completed suicides. Compared to never-users, HC users had a relative risk of 1.97 (95% CI: 1.85-2.10) for a suicide attempt, and the risk for completed suicide was more than tripled (RR 3.08)[26]. As with the depression data, the incidence peaked precisely two months after initiation and was highest among the adolescent demographic[26].

Critics of observational data frequently cite "healthy user bias" and "familial confounding." The primary counterargument is that women who seek HCs may engage in earlier sexual activity or possess different socioeconomic stressors that independently cause depression, thereby confounding the data. To definitively address this, Johansson et al. (2023) published a study in *Epidemiology and Psychiatric Sciences* analyzing 264,557 women from the UK Biobank[30].

Uniquely, this study utilized a sibling pair analysis (N=7,354 pairs) to rigorously control for shared genetic and environmental confounds[30]. They found that the first two years of OC use were associated with an increased hazard ratio (HR) for depression of 1.71 (95% CI: 1.55-1.88) compared to never-users[30]. The sibling analysis confirmed that the relationship between OC use and depression is causal, not merely correlational[31].

Furthermore, Anderl et al. (2020), in the *Journal of Child Psychology and Psychiatry*, demonstrated that adolescent OC use predicts a lasting vulnerability to major depressive disorder (MDD) in early adulthood (OR = 1.41), even years after the medication has been discontinued[33]. This finding has profound implications, suggesting that suppressing the HPG axis with synthetic hormones may permanently alter brain organization during the critical, highly plastic window of pubertal neurodevelopment[35].

The Contradiction of Randomized Controlled Trials (RCTs)

To isolate causality outside of observational settings, Zethraeus et al. (2017) and Lundin et al. (2017) published rigorous double-blind, placebo-controlled RCTs in *Psychoneuroendocrinology*. Their findings highlight the "averages versus individuals" paradox.

Zethraeus et al. (2017) randomized 340 healthy women to either a placebo or a widely used second-generation COC (150 µg levonorgestrel / 30 µg ethinyl estradiol) for a duration of three months[7]. They found a significant reduction in general well-being among pill users, specifically driven by statistically significant drops in self-control, vitality, and positive well-being on the Psychological General Well-Being Index (PGWBI)[7]. However, there was *no significant difference* in mean depressive scores on the Beck Depression Inventory (BDI) between the treatment and placebo groups[7].

Similarly, Lundin et al. (2017) randomized 202 women to a placebo or a COC (1.5 mg estradiol / 2.5 mg nomegestrol acetate)[39]. Utilizing the Daily Record of Severity of Problems (DRSP), the researchers found that the COC group showed small but statistically significant mean increases in intermenstrual anxiety (mean change +0.22), irritability (+0.23), and mood swings (+0.15)[7]. Yet, these increases were coupled with premenstrual *improvement* in mood. Again, mean depression scores (MADRS) did not shift radically across the entire cohort[39].

Reconciling the Data: Averages vs. Individuals

The leading critics of the massive registry findings—including several prominent gynecological and psychiatric bodies—point to the *absolute risk* to contextualize the alarmist relative risks. While a relative risk of 1.23 to 2.2 sounds terrifying, the absolute baseline risk of depression is low. Skovlund (2016) explicitly noted that non-users had an incidence rate of 1.7 per 100 woman-years for first antidepressant use, which increased to 2.2 per 100 woman-years in users. This equates to an additional one woman prescribed antidepressants for every 200 users[22].

Similarly, examining the dose-response of the LNG-IUS, Skovlund showed 1-year absolute risks of clinical depression at 1.21% for the low dose (13.5mg), 1.46% for the medium dose (19.5mg), and 1.84% for the high dose (52mg)[42].

The paradox between the massive registry findings (showing undeniable harm) and the null mean findings in RCTs is reconciled by recognizing response heterogeneity. The "average" woman on the pill does not become clinically depressed. Rather, a specific, highly susceptible

subgroup—often adolescents, women with prior psychiatric histories, or those with genetic vulnerabilities (e.g., the aforementioned *FKBP5* polymorphism)—experiences severe, clinically significant mood deterioration[16]. In an RCT, the severe depressive reactions of this minority are statistically washed out by the majority who experience no effect, alongside a subset of women who experience profound mood stabilization (particularly those suffering from underlying premenstrual dysphoric disorder, or PMDD)[7]. Therefore, assessing HC safety based purely on a population mean is a statistical fallacy that obscures severe individual harm.

Cognition: Spatial and Verbal Dynamics

The natural menstrual cycle is traditionally associated with subtle cognitive fluctuations: high endogenous estradiol environments (late follicular) occasionally correlate with enhanced verbal memory and fluency, while low estradiol environments (menses) correlate with enhanced male-typical spatial performance, such as mental rotation tasks.

Comprehensive reviews by Hampson (2020) in *Frontiers in Neuroendocrinology* and Griksiene et al. demonstrate that HC effects on cognition heavily depend on the androgenic profile of the specific synthetic progestin used[47]. COCs containing first- or second-generation progestins (e.g., levonorgestrel), which are highly androgenic, tend to mildly diminish accuracy on spatial tasks like the Vandenberg Mental Rotations Test (MRT) while modestly improving verbal fluency[47].

Conversely, anti-androgenic progestins (e.g., drospirenone, commonly found in brands like Yaz) exhibit entirely different cognitive profiles. Studies indicate that anti-androgenic formulations sometimes result in lower performance in hippocampus-related domains (such as verbal memory and visuospatial ability) but actually enhance performance in frontal-lobe-dependent executive tasks, such as cognitive inhibition[50]. Thus, "the pill" is not a cognitive monolith; its cognitive signature is highly variable, dictated by the specific pharmacological ratio of estrogenic to progestational activity[48]. These findings have generally replicated, though effect sizes remain small and rarely impact daily occupational functioning.

Sexual Desire and Functioning

The effect of HCs on female sexual desire is a complex interplay of biochemistry and psychology. Physiologically, oral contraceptives suppress ovarian androgen (testosterone) production. More importantly, the synthetic estrogen heavily stimulates the hepatic synthesis of Sex Hormone-Binding Globulin (SHBG), increasing its circulating levels by 80% to 300%[51]. This massive influx of SHBG effectively binds circulating free testosterone, rendering it biologically inactive and thereby dampening libido in a subset of women.

A definitive systematic review by Pastor et al. (2013), published in the *Journal of Sexual Medicine*, indicates that while the majority of women (over 80%) report no change in libido, approximately 15% of COC users report a clinically significant decrease in sexual desire[20]. Furthermore, formulations containing anti-androgenic progestins (like drospirenone) affect desire, arousal, and vaginal lubrication more negatively than androgenic formulations (like levonorgestrel)[52]. Zethraeus et al. (2017) confirmed this in their RCT, noting a statistically significant but dimensionally minute median decrease in sexual interest (-2.0 vs -1.0 on a psychometric scale) among COC users compared to placebo[53].

However, behavioral outcomes are mediated by psychological relief. The removal of pregnancy anxiety, the reduction of dysmenorrhea (menstrual cramps), the mitigation of heavy bleeding, and the suppression of endometriosis pain frequently result in an *increase* in sexual frequency, spontaneity, and satisfaction for many women. For these women, the psychological benefits of reproductive control completely counterbalance the biochemical suppression of free testosterone[20].

Mate Choice, Partner Preference, and The Congruency Hypothesis

One of the most fiercely debated topics in evolutionary psychology over the past two decades is whether the pill alters mate choice. According to the cycle-shift hypothesis, naturally cycling women at peak fertility (the ovulatory phase) exhibit a heightened preference for indicators of male genetic fitness and high testosterone—such as facial masculinity, vocal depth, dominance behaviors, and Major Histocompatibility Complex (MHC) dissimilarity[18]. Because HCs suppress ovulation and eliminate the fertile window, it is hypothesized that HC users default to a continuous luteal-phase preference, favoring less masculine, more prosocial, nurturing, and genetically similar male phenotypes[56].

This evolutionary framework birthed the **Congruency Hypothesis**, formally tested by Roberts et al. (2014) in *Psychological Science*. The hypothesis posits that if a woman meets her partner while on the pill, her neurological mate-preference systems are tuned to a specific, less-masculine phenotype. If she subsequently discontinues the pill (for instance, to conceive a child), her restored endogenous hormonal cycle alters her preferences. Such women, the hypothesis claims, will suddenly find their partners less sexually attractive (though perhaps highly reliable as providers), leading to a stark drop in relationship and sexual satisfaction[55]. Marcinkowska et al. (2018) tested this in a large cross-cultural sample. While they did not find robust support for massive, relationship-ending drops in satisfaction, they did find that women who changed their HC status (non-congruent users) reported slightly lower passion and sexual satisfaction than consistent users or non-users[57].

The Controversy and the Critics: The cycle-shift mate-choice theory has recently been subjected to intense critical scrutiny and replication crises. The leading critic in this domain is Julia Stern and colleagues (2019, 2021). In highly powered, rigorous, pre-registered replications published in *Psychoneuroendocrinology*, Stern found *no* robust evidence that oral contraceptives systematically shift women's preferences for facial masculinity[58]. Similarly, Ranehill and Zethraeus (2018) found that HCs do not impact broader economic or behavioral preferences in a randomized trial[37]. Currently, while the theoretical basis for altered mate choice via MHC alignment and oxytocin blunting remains biochemically plausible, large-scale behavioral replications have cast severe doubt on the clinical and real-world significance of the so-called "pill goggles" phenomenon. The consensus is shifting toward viewing mate choice as overwhelmingly driven by sociocultural and interpersonal factors, heavily dwarfing any subtle endocrine nudges.

The Cultural Layer: Societies and the Endocrine Shift

The cultural layer sits atop the physiological and behavioral layers, representing the macro-level societal outcomes of the technology. The advent of hormonal contraception triggered a cultural

revolution. By allowing women to reliably and independently delay childbearing, HCs facilitated the equalization of educational attainment and labor force participation between the sexes. Culturally, the pill changed the architecture of courtship, dating, and marriage. It elongated the period of adolescence and young adulthood during which individuals engage in sexual relationships without reproductive consequences. However, this has also resulted in a paradigm where a large proportion of women navigate critical neurodevelopmental windows (puberty and adolescence) and major life decisions (choosing a lifelong partner, establishing a career) under a synthetic endocrine state. As the physiological data conclusively shows, this state is characterized by blunted HPA stress responses, suppressed oxytocin reward pathways, and altered resting-state brain connectivity.

The cultural implication is inherently paradoxical: the profound sociopolitical empowerment and bodily autonomy granted by HCs exist precisely alongside subtle, population-wide shifts in affect, stress processing, and relational neurochemistry.

Conclusions

10-Line Summary of Robust Findings

1. Hormonal contraceptives (HCs) act on the brain by suppressing the endogenous HPG axis and introducing synthetic steroids that alter resting-state functional connectivity, notably in the default mode and executive control networks.
2. HC use dampens amygdala reactivity to negative emotional stimuli and blunts the HPA axis salivary cortisol response to acute psychosocial stress (demonstrated in TSST paradigms).
3. Large registry studies confirm a causal, elevated risk of first-time depression and antidepressant use, with relative risks highest among adolescents (1.8 to 2.2).
4. Sibling-controlled analyses (e.g., UK Biobank) confirm this depression risk is causal and not solely an artifact of healthy user bias or familial confounding, particularly in the first two years of use.
5. The absolute risk of clinical depression remains low (e.g., an additional 1 in 200 users), indicating that severe mood effects are concentrated in genetically or psychiatrically vulnerable subgroups.
6. HCs elevate hepatic Sex Hormone-Binding Globulin (SHBG) and suppress free testosterone, resulting in decreased sexual desire in approximately 15% of users, though over 80% report no change.
7. The cognitive profile of a user (e.g., spatial reasoning vs. verbal fluency) is subtly modified depending on the specific androgenic or anti-androgenic properties of the progestin used.
8. Exogenous hormones blunt oxytocin-mediated neural reward responses to romantic partners, providing a physiological basis for altered attachment dynamics.
9. While the "Congruency Hypothesis" suggests that starting or stopping the pill alters mate choice and sexual satisfaction, massive recent replications show these effects are weak or non-existent in real-world facial masculinity preferences.
10. The average statistical null-effects regarding depression found in double-blind RCTs obscure profound, overlapping individual responses that range from severe dysphoria to highly beneficial mood stabilization.

Contested or Open Questions

- **The Mate Choice Debate:** Do oral contraceptives definitively alter women's mate selection criteria (the Congruency Hypothesis), or are earlier evolutionary psychology findings failing to replicate (as argued by Stern and colleagues)?
- **Suicidality vs. Confounding:** While Skovlund (2018) found a tripled relative risk of suicide, to what extent do unmeasured environmental or psychosocial stressors related to early sexual debut in adolescence confound this extreme outcome, despite propensity score matching?
- **Long-Term Neurodevelopment:** Does the initiation of HCs during early puberty permanently alter the developmental trajectory of the prefrontal cortex and amygdala, explaining the lasting vulnerability to MDD in adulthood identified by Anderl (2020)?
- **Progestin Variations:** How do newer, fourth-generation anti-androgenic progestins (like drospirenone) or natural estrogens (estetrol) differentially impact central nervous system connectivity compared to older, highly androgenic progestins (like levonorgestrel)?
- **Predictive Biomarkers:** Can genetic screenings (such as for the *FKBP5* rs1360780 polymorphism) be clinically operationalized to accurately predict which women will suffer severe psychiatric side effects before prescribing HCs?

5 to 10 Most Important Sources to Read in Full

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2. **Johansson, T., et al. (2023).** *Population-based cohort study of oral contraceptive use and risk of depression.* Epidemiology and Psychiatric Sciences. (Provides crucial sibling-pair analysis confirming causality).
3. **Zethraeus, N., et al. (2017).** *A first-choice combined oral contraceptive influences general well-being in healthy women: a double-blind, randomized, placebo-controlled trial.* Psychoneuroendocrinology. (The gold-standard RCT demonstrating changes in well-being without shifting mean depression scores).
4. **Pletzer, B., et al. (2023).** *Triple network model of brain connectivity changes related to adverse mood effects in an oral contraceptive placebo-controlled trial.* Translational Psychiatry. (Maps the exact brain connectivity alterations caused by the pill in relation to mood).
5. **Anderl, C., et al. (2020).** *Oral contraceptive use in adolescence predicts lasting vulnerability to depression in adulthood.* Journal of Child Psychology and Psychiatry. (Details the critical pubertal neurodevelopmental window).
6. **Hertel, J., et al. (2017).** *Evidence for Stress-like Alterations in the HPA-Axis in Women Taking Oral Contraceptives.* Scientific Reports. (Uncovers the FKBP5 genetic and cortisol resistance mechanism).
7. **Scheele, D., et al. (2016).** *Oxytocin Enhances Brain Reward System Responses in Men Viewing the Face of Their Female Partner.* PNAS. (Demonstrates the blunting of oxytocin pair-bonding in HC users).
8. **Stern, J., et al. (2021).** *Do oral contraceptives alter mate preferences?*

Psychoneuroendocrinology. (The leading critical paper debunking earlier mate-choice shift theories).
9. **Lundin, C., et al. (2017).** *Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle.* Psychoneuroendocrinology. (Highlights the dual nature of HC mood effects in an RCT).
10. **Pastor, Z., et al. (2013).** *The influence of combined oral contraceptives on female sexual desire: A systematic review.* The Journal of Sexual Medicine. (The definitive synthesis on libido and SHBG mechanisms).

Implications for living together

Note: The following analysis strictly avoids the naturalistic fallacy; an unmedicated, natural physiological state is not inherently "good" or "better" than a medicated one, as natural hormone fluctuations frequently cause severe, debilitating distress (e.g., PMDD, dysmenorrhea).

For couples, families, and societies, the realization that hormonal contraceptives exert systemic neuroendocrine effects demands a paradigm shift in how we manage relationship dynamics and reproductive health. At the interpersonal level, partners must recognize that initiating or discontinuing hormonal contraception can induce genuine, biochemically driven shifts in mood, emotional processing, libido, and stress tolerance. Relationship friction, drops in sexual intimacy, or emotional distancing arising shortly after a change in contraceptive status should be viewed through a neurobiological lens rather than purely a psychological or relational one. Depersonalizing these shifts as pharmacological side-effects can prevent the deterioration of otherwise healthy partnerships.

At the family and organizational level, the data strongly suggests exercising high caution when prescribing HCs to adolescents. Because the adolescent brain is actively myelinating and forming regulatory circuits within the prefrontal cortex and amygdala, introducing HPA-suppressing and emotion-blunting synthetics during this precise window carries an elevated, causal risk of triggering depressive episodes that may persist into adulthood. Parents, educators, and clinicians should engage young women in comprehensive risk-benefit analyses. Where appropriate, prioritizing non-hormonal methods (like copper IUDs) or ultra-low-dose systemic options is vital, particularly if the patient possesses a familial history of mood disorders. Ultimately, society must integrate the fact that women have carried the exclusive neurological and physiological burden of modern pharmacological family planning, necessitating both deep clinical empathy and accelerated funding for alternative male contraceptives to balance the biological scales of living together.

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