



Physiological, Psychological, and Clinical Effects of Oral Contraceptive Pills: A Systematic Narrative Synthesis

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ABSTRACT

Combined and progestogen-only oral contraceptive pills (OCPs) are among the most widely used reversible methods of fertility control worldwide, yet their physiological and psychological effects remain debated across multiple clinical domains. This manuscript synthesizes findings from seventeen recent publications—systematic reviews, meta-analyses, randomized trials, cohort studies, and cross-sectional surveys—covering the cognitive, cardiovascular, metabolic, musculoskeletal, psychological, and reproductive effects of OCPs, together with their history, therapeutic applications, and emerging formulations. Effects prove domain- and formulation-specific: OCP use is associated with modest gains in verbal memory, while venous thromboembolism risk and inflammatory markers vary by progestin generation and androgenic activity. Findings on mortality, mood, and exercise-related muscle damage are similarly mixed, and methodological heterogeneity across the literature limits firm conclusions in several domains. Non-contraceptive use—particularly for menstrual disorders and polycystic ovary syndrome—is common and clinically valuable, although weight-related concerns remain a leading driver of discontinuation. This synthesis supports individualized, progestin-informed prescribing and identifies persistent gaps in long-term, high-quality comparative evidence.

Keywords: oral contraceptives; combined oral contraceptive pills; progestins; venous thromboembolism; cognition; polycystic ovary syndrome; systematic review

*Corresponding Author Name: Dr Dhanavanti Runwal
Received 1 July 2026, Accepted 26 July 2026

Please cite this article as: Runwal D *et al.*, Physiological, Psychological, and Clinical Effects of Oral Contraceptive Pills: A Systematic Narrative Synthesis. American Journal of Pharmacy & Health Research 2026.

INTRODUCTION

Oral contraceptive pills occupy a central place in reproductive healthcare worldwide. Combined oral contraceptives are among the most commonly prescribed medications for women of reproductive age [1], used both to prevent pregnancy and to manage a range of gynecological and systemic conditions. Despite more than six decades of accumulated research, active debate persists regarding their effects on cognition, cardiovascular risk, metabolic function, and mental health, reflecting the biological complexity of steroid hormone action and the methodological challenge of studying a heterogeneous medication class across diverse populations and formulations.

Reliable contraception reduces unintended pregnancy and its associated maternal morbidity, and underpins broader goals of reproductive autonomy and family planning. Because oral contraceptive pills are self-administered, low-cost, and require no procedure, they remain accessible across a wide range of health-system contexts—from well-resourced settings with regular clinical follow-up to lower-resource settings where sustained access to contraceptive counseling may be limited. This accessibility means that any adverse effect identified in the research literature has the potential to affect a very large population of users.

The modern oral contraceptive traces its origins to the mid-twentieth century, when reproductive rights advocates Margaret Sanger and Katherine McCormick, biologist Gregory Pincus, and gynecologist John Rock translated early animal research on ovulation-suppressing steroids into a clinically usable product [2]. Early formulations carried substantially higher doses of estrogen and progestin than are used today; reports of thromboembolic and other adverse events—crystallized by influential 1977 publications linking the pill to thromboembolism-related mortality—prompted a sustained effort to reformulate the product [2, 11]. Over subsequent decades, ethinyl estradiol content was progressively reduced and successive generations of progestins, each with a distinct androgenic, antiandrogenic, antiestrogenic, and mineralocorticoid profile, were introduced to improve safety while preserving contraceptive efficacy [11].

So-called "pill scares"—periods of intense media and clinical attention to a specific safety concern—have, on more than one occasion, been followed by declines in oral contraceptive use and measurable increases in unintended pregnancy and abortion [11]. This pattern shows that the population-level consequences of contraceptive safety communication extend well beyond the specific adverse event being reported, and that clear, proportionate communication of formulation-specific risk is itself a matter of public health importance.

Combined oral contraceptives act principally by suppressing the hypothalamic–pituitary–gonadal axis: synthetic estrogen and progestin together blunt gonadotropin-releasing hormone activity, reducing follicle-stimulating hormone and luteinizing hormone output and thereby preventing the luteinizing hormone surge required for ovulation [9]. Progestogen-only formulations rely more heavily on cervical mucus thickening and endometrial changes, with the degree of ovulation suppression varying by dose and by individual; data on a low-dose norgestrel-only pill indicate that a substantial proportion of users continue to show ovarian follicular activity even without full ovulation, indicating that ovulation inhibition exists on a spectrum rather than as an all-or-nothing phenomenon [4].

Although developed and regulated primarily as a contraceptive, the oral contraceptive pill has become a first-line therapeutic tool for numerous non-contraceptive indications. Population-level prescribing data from Europe indicate that a substantial share of combined oral contraceptive prescriptions—particularly in some national contexts—are written wholly or partly for therapeutic purposes, most often to manage menstruation-related disorders [7]. Combined formulations are similarly central to the management of polycystic ovary syndrome (PCOS), where they regulate cycles and reduce biochemical and clinical hyperandrogenism; comparative trials increasingly examine how differences in progestin generation and antiandrogenic activity influence outcomes such as hirsutism, body mass index, and androgen levels in this population [14]. Major international guidelines recommend combined pills as a foundational PCOS treatment, and ongoing research continues to refine which progestin formulations offer the most favorable balance of therapeutic benefit and cardiovascular safety [14]. Because women with PCOS often already carry elevated baseline metabolic and thrombotic risk, this population is a particularly informative lens for examining how progestin-specific effects should inform individualized prescribing, a theme that recurs throughout this synthesis.

Tolerability is central to the real-world impact of oral contraceptive pills, since perceived side effects are a major determinant of continuation. Concerns about weight gain and mood changes are commonly cited reasons for discontinuation, and these concerns are not evenly distributed: women with higher body mass index are more likely to attribute weight change to pill use and to discontinue on that basis [15]. Community-based survey data from South Asia similarly document a wide range of self-reported adverse effects alongside continued reliance on combined formulations, reflecting the tension between contraceptive effectiveness and lived tolerability [13].

Researchers also continue to explore delivery paradigms intended to better match contraceptive dosing with women's actual patterns of sexual activity. Scoping reviews of an on-demand, pericoital oral contraceptive—taken around the time of intercourse rather than daily—find considerable international interest, particularly among younger and more educated women and those with infrequent intercourse, tempered by knowledge gaps among both users and providers and by persistent misconceptions about the fertility effects of hormonal contraception [5].

Several dimensions of oral contraceptive use remain genuinely unsettled. Systematic reviews of cognitive outcomes report a modest, fairly consistent benefit for verbal memory but inconsistent, formulation-dependent effects on visuospatial ability [1]. Cardiovascular epidemiology continues to refine estimates of venous thromboembolism (VTE) risk by progestin type, generally finding higher risk with newer progestins relative to levonorgestrel [10]. Long-running cohort data addressing overall mortality present a reassuring picture for all-cause death but raise less-explained associations with specific causes of death—associations that merit cautious interpretation, given that they largely reflect older, higher-dose formulations [8]. Newer lines of inquiry into iron and inflammatory biomarkers [6], exercise-induced muscle damage [12], and mood outcomes [17] add further texture, and further uncertainty, to the overall risk–benefit picture.

Mood is a domain in which public concern has, at times, outpaced the underlying evidence. Reports linking hormonal contraception to depression have received considerable attention in clinical and popular discourse and shape how patients weigh the decision to start or continue use. Because mood-related concerns are cited frequently as reasons for dissatisfaction, and because affective symptoms are inherently harder to measure objectively than a thromboembolic event or a laboratory biomarker, this domain illustrates the gap that can open between subjective patient experience and what controlled research is able to detect [13, 17].

A theme that recurs across these otherwise disparate literatures is the pharmacological heterogeneity of the progestin component. Because individual progestins differ in androgenic, antiandrogenic, and other steroid-receptor activities, studies that treat "oral contraceptives" as a single homogeneous exposure risk obscuring clinically meaningful differences between formulations [11]. This heterogeneity also complicates the study of drug–drug interactions, since the range of estrogen doses and progestin metabolic pathways on the market makes it difficult to generalize interaction data from one formulation to another—a challenge that has prompted calls for more systematic, pharmacokinetically grounded approaches to interaction study design [3].

The seventeen sources drawn upon in this synthesis illustrate how methodologically varied contemporary oral contraceptive research has become. They include large systematic reviews and meta-analyses, prospective cohorts followed for decades, physiological studies involving hormone measurement and ultrasonography, small mechanistic trials in exercise physiology, and cross-sectional surveys capturing patient-reported experience. Each design answers a different question and carries different strengths and limitations: cohort studies such as the Nurses' Health Study offer long follow-up and large sample sizes but reflect the formulations available at enrollment [8]; small physiological studies offer mechanistic precision but limited generalizability [4, 12]; and cross-sectional surveys capture lived experience but remain vulnerable to recall bias [13, 15]. Appreciating this diversity of methods is a prerequisite for interpreting the sometimes-conflicting findings summarized below.

Several of the individual sources are themselves systematic reviews or meta-analyses confined to a single domain, such as cognition, VTE, or PCOS management [1, 10, 14]. Such focused reviews generate rigorous, domain-specific evidence but are not designed to reveal patterns that cut across domains, such as the recurring role of progestin generation as an effect modifier, or contrasts between objective safety data and subjective patient-reported tolerability. A cross-domain synthesis is therefore complementary rather than competing: it does not replace the rigor of focused systematic reviews but draws out connections between them that would not otherwise be visible.

Given this breadth of evidence—produced using different study designs, populations, and outcome measures—there is value in drawing findings together across domains rather than treating each in isolation. The present manuscript undertakes such a synthesis, drawing on seventeen recent publications addressing the cognitive, cardiovascular, metabolic, musculoskeletal, reproductive, psychological, and pharmacological dimensions of oral contraceptive pill use, together with their historical development and therapeutic applications. The aim is threefold: to map the current evidence landscape across these domains; to identify recurring effect modifiers, particularly progestin type and generation; and to highlight areas where the existing evidence base remains too heterogeneous or too limited to support definitive clinical guidance.

MATERIALS AND METHOD

This manuscript is a narrative, thematically organized synthesis rather than a quantitative statistical meta-analysis. The source material comprises seventeen previously identified, peer-reviewed publications on oral contraceptive pills, compiled as article abstracts covering

systematic reviews and meta-analyses, randomized and prospective cohort studies, retrospective cohort analyses, cross-sectional surveys, and narrative or expert-opinion reviews. Because these sources differ substantially in study design, target population, exposure definition (for example, combined versus progestogen-only formulations, or specific progestin types), and outcome measures (ranging from cognitive test scores to biomarker concentrations to categorical mortality outcomes), formal statistical pooling of effect estimates—the defining feature of a quantitative meta-analysis—was neither methodologically appropriate nor possible from abstract-level data alone.

Each source was reviewed and grouped into a thematic domain based on its primary outcome: cognition, cardiovascular risk, metabolic and inflammatory markers, musculoskeletal effects, reproductive and ovulatory physiology, mood, patient-reported tolerability, drug interactions, historical development, and therapeutic applications. Findings within each domain were synthesized narratively, and cross-cutting patterns—most notably the recurring influence of progestin type and generation—were identified across domains. All content presented reflects an independent paraphrase and synthesis of the source abstracts; no source text has been reproduced verbatim.

This approach carries limitations. The synthesis is based on abstract-level information rather than full-text critical appraisal, so methodological quality and risk of bias could not be independently assessed for most sources. Several source documents were themselves systematic reviews, so some overlap in underlying primary studies across domains is possible. The conclusions offered here should therefore be read as a structured overview of the current evidence landscape rather than as a formal, quantitatively pooled meta-analytic estimate of effect.

RESULTS AND DISCUSSION

Table 1 summarizes the design, population, and principal finding of each of the seventeen sources included in this synthesis, organized by physiological or clinical domain.

Table 1: Overview of included sources by domain.

Sr.no	Domain	Study design / sample	Key finding
1	Cognition	Systematic review; 22 studies	Modest, consistent improvement in verbal memory; visuospatial effects vary with progestin androgenicity; overall evidence quality poor.
2	Historical development	Narrative review	Traces the pill's evolution from 1960s high-dose formulations to modern low-dose, diverse-progestin products.
3	Drug–drug interactions	Methodological review	Highlights PK/PD complexity across formulations; recommends PK-based interaction studies supported by

4	Ovulation suppression (POP)	Prospective randomized crossover; analyzed	51	physiologically based PK modeling. About two-thirds showed no ovulation in the first cycle; persistent follicles were common among the remainder.
5	On-demand pericoital pill	Scoping review; papers, countries	30 16	Substantial international user appeal, especially among younger women and those with infrequent intercourse; knowledge and access barriers remain.
6	Iron / inflammatory markers	Cross-sectional; n=100		Elevated ferritin and C-reactive protein in users vs. non-users, more pronounced with higher body weight.
7	Therapeutic prescribing	Multinational cohort (PRO-E2); n=91,313		Substantial share of combined-pill prescriptions are therapeutic rather than purely contraceptive, especially in Italy; menstrual disorders are the leading driver.
8	Mortality	Prospective cohort (Nurses' Health Study); n=121,701; 36-yr follow-up		No difference in all-cause mortality; possible association with violent/accidental death; reflects older, higher-dose formulations.
9	Reproductive physiology	Narrative review		Describes hypothalamic–pituitary–gonadal axis mechanism; notes potential hormone-imbalance-related effects with long-term use.
10	VTE risk by progestin	Systematic review / meta-analysis; studies	22	Non-levonorgestrel progestins associated with 1.5–2.0× higher VTE risk versus levonorgestrel-containing pills.
11	History of side effects	Narrative / expert-opinion review		Chronicles estrogen-dose reduction following 1977 thromboembolism findings; each progestin carries a distinct receptor-activity profile.
12	Musculoskeletal effects	Controlled study; 9 users, 9 non-users	9	Users showed a greater creatine kinase rise after eccentric exercise; no difference in tendon properties.
13	Regional survey (India)	Cross-sectional survey; n=30		Documents a broad side-effect burden and reduced quality of life, without a clear change in depressive symptoms.
14	PCOS / COCP comparison	Systematic review / meta-analysis; RCTs	19	Fourth-generation pills associated with lower BMI/testosterone than third-generation; EE/CPA best for hirsutism but not recommended first-line due to VTE risk.
15	Weight gain & discontinuation	Cross-sectional survey (NSFG); n=3,709		About 35% discontinue due to dissatisfaction; overweight/obese women more likely to cite weight gain.
16	Metabolic effects (IVF context)	Narrative review		Notes parallels between contraceptive and IVF hormone effects on glucose/lipid metabolism and inflammation.
17	Mood/depression (PCOS)	Cross-sectional; Thai women; n=96		No significant association between pill use and depression; low testosterone linked to depression risk.

Three broad patterns emerge from this overview. First, effects tend to be outcome-specific rather than uniform: cognition, venous thromboembolism risk, and PCOS-related metabolic parameters each show a measurable, direction-consistent signal, whereas mortality and mood outcomes are

largely reassuring in the specific contexts studied. Second, progestin identity and generation is the most frequently recurring effect modifier, surfacing independently in the cognitive, cardiovascular, and PCOS-treatment literatures. Third, patient-reported tolerability—weight change, mood, and general side-effect burden—drives real-world discontinuation somewhat independently of objective safety findings, pointing to a gap between clinical safety profiles and lived user experience. These patterns are examined by domain in the section that follows.

DISCUSSION

Cognitive Effects

The most consistent cognitive finding associated with oral contraceptive use is a modest improvement in verbal memory performance, replicated across studies despite substantial methodological heterogeneity [1]. Effects on other domains, particularly visuospatial ability, are less consistent and appear to depend on the androgenic activity of the progestin component, suggesting that formulation-specific hormonal profiles—rather than oral contraceptive use as a single exposure—better explain cognitive variability between studies [1]. Because the underlying evidence base is of generally poor methodological quality, these findings should be regarded as hypothesis-generating rather than conclusive, and future cognitive research should stratify explicitly by progestin type.

Cardiovascular and Thromboembolic Risk

Venous thromboembolism risk is one of the better-characterized safety concerns associated with combined oral contraceptives, and the evidence converges on a clear, formulation-dependent pattern: progestins such as desogestrel, drospirenone, gestodene, and cyproterone acetate carry meaningfully higher VTE risk than levonorgestrel [10], a finding that has held across the historical evolution of pill formulations even as estrogen doses fell following early thromboembolism scares [11]. This consistency—across a dedicated VTE meta-analysis and a broader historical review of pill safety—supports the clinical practice of preferring levonorgestrel-containing formulations for women with elevated baseline thrombotic risk, and shows how a single adverse signal, the 1977 thromboembolism mortality reports, reshaped an entire product class over subsequent decades.

Mortality

Long-term cohort data, most notably from the Nurses' Health Study, show no excess all-cause mortality among ever-users of oral contraceptives relative to never-users, an important counterweight to domain-specific safety signals [8]. The same data suggest a positive association between oral contraceptive use and violent or accidental death, and reduced ovarian cancer

mortality; the causal interpretation of these associations remains unclear, and their relevance to contemporary practice is limited by the fact that the underlying exposure reflects older, higher-dose formulations rather than the lower-dose products in common use today [8]. Cohorts large and long enough to detect rare cause-specific mortality differences necessarily enroll participants years or decades before analysis, so the exposure measured often lags behind current prescribing—a gap that should temper how directly historical mortality findings are applied to contemporary counseling.

Metabolic and Inflammatory Effects

Evidence linking oral contraceptive use to elevated ferritin and C-reactive protein raises the possibility of a low-grade chronic inflammatory state associated with long-term use, an effect that appears more pronounced among users with higher body weight [6]. Evidence from the assisted-reproduction literature, noting that hormonal therapies including oral contraceptives may impair glucose and lipid metabolism and promote insulin resistance, situates these findings within a broader pattern of steroid hormone effects on metabolic physiology [16]. Metabolic and inflammatory monitoring may therefore be particularly relevant for oral contraceptive users who are overweight or obese, though the clinical significance of these biomarker changes for long-term health outcomes remains to be established.

Musculoskeletal Effects

A smaller line of evidence examines musculoskeletal responses to exercise in oral contraceptive users. One controlled study found a significantly greater creatine kinase rise after eccentric exercise in users compared with non-users, with no measurable difference in patella tendon properties, suggesting an estrogen-mediated effect on muscle damage and repair rather than a tendon-specific mechanism [12]. Based on a small sample, this finding is consistent with broader evidence that sex hormone fluctuations influence exercise physiology, and it has practical relevance for recovery from unaccustomed eccentric exercise among active oral contraceptive users.

Ovulatory Suppression and Reproductive Physiology

Direct physiological monitoring of a progestogen-only norgestrel pill shows that ovulation suppression is neither universal nor binary: roughly two-thirds of participants showed no evidence of ovulation during the initial treatment cycle, while a substantial share of the remainder exhibited ongoing follicular activity, including persistent follicles, without full ovulation [4]. This mechanism-level evidence complements the broader physiological framework describing how combined and progestogen-only pills act on the hypothalamic–pituitary–gonadal

axis [9], and shows that ovulation inhibition operates along a continuum of follicular quiescence, development, and incomplete suppression rather than as a uniform on/off effect.

Therapeutic Applications and PCOS Management

Beyond contraception, oral contraceptives are extensively used for menstruation-related disorders, a pattern especially pronounced in some national contexts according to European prescribing data [7]. In PCOS specifically, comparative trial evidence indicates that newer-generation combined pills and antiandrogenic formulations, such as ethinyl estradiol with cyproterone acetate, offer measurable advantages for hyperandrogenism-related outcomes like hirsutism and testosterone levels, yet guideline bodies remain reluctant to recommend these formulations first-line given their elevated thrombotic risk [14]. This reflects a recurring tension between condition-specific therapeutic benefit and systemic safety: the formulation with the best outcome for a given metabolic or dermatologic endpoint in PCOS is not necessarily the formulation a prescriber should recommend first, once thrombotic risk is weighed alongside benefit—reinforcing that progestin selection in this population should be individualized rather than guided by a single outcome in isolation.

Mood and Psychological Outcomes

Contrary to persistent public concern that oral contraceptives increase depression risk, a cross-sectional study in Thai women with PCOS found no significant difference in depression prevalence between users and non-users, with low testosterone—rather than pill use itself—emerging as the stronger correlate of depressive symptoms in this population [17]. This finding is drawn from a modest sample in a specific clinical population and should be read alongside regional survey data suggesting that oral contraceptive use is associated with broader quality-of-life reductions even when depressive symptoms specifically are not affected [13], indicating that mood-adjacent constructs—irritability, body image, general well-being—may be more sensitive to pill-related change than clinical depression measures alone.

Patient-Reported Outcomes and Discontinuation

Real-world continuation of oral contraceptive pills depends as much on perceived tolerability as on objective safety data. Survey evidence indicates that roughly a third of users discontinue combined pills due to general dissatisfaction, with side effects—especially weight gain—cited disproportionately by women with overweight or obesity, even though the overall proportion of users reporting weight gain is relatively modest [15]. Regional survey data document a broad range of self-reported adverse effects, including menstrual changes, breast tenderness, and mood-related complaints, alongside continued reliance on combined formulations as a preferred

method [13]. Counselling that proactively addresses weight- and mood-related concerns, particularly among higher-BMI patients, could meaningfully improve continuation rates. The gap between the modest proportion of users reporting objective weight change and the larger proportion citing weight concerns as a reason for stopping suggests that anticipatory counselling—not only clinical management of side effects once they occur—may be an underused lever for improving satisfaction and continuation.

Emerging Formulations and Access

The scoping review of on-demand, pericoital oral contraceptive pills points to substantial unmet need for methods that better align with women's actual, sometimes infrequent or unplanned, patterns of sexual activity [5]. Interest in such a product spans diverse demographic groups internationally, though uptake is likely to be constrained by the same knowledge gaps and provider-level unfamiliarity that have historically slowed acceptance of new contraceptive technologies, as well as persistent myths regarding the fertility effects of hormonal contraception [5]. Contraceptive innovation therefore remains an ongoing and unresolved area of reproductive health research and policy, particularly for regions such as Southeast Asia and the Pacific that remain underrepresented in the current evidence base.

Pharmacological Complexity and Drug Interactions

The methodological review of oral contraceptive drug–drug interactions underscores a challenge that runs beneath many of the domain-specific findings above: the diversity of available formulations—differing in estrogen dose and progestin metabolic pathway—makes it difficult to generalize interaction, safety, or efficacy data from one product to another [3]. The recommendation to prioritize pharmacokinetically grounded study designs, supported by physiologically based PK modeling, reflects a broader methodological maturation in this field and offers an approach that could usefully extend to other domains, such as cognitive or metabolic research, where formulation-level heterogeneity currently limits the interpretability of pooled findings [3].

Cross-Cutting Methodological Limitations

Several limitations recur across this body of evidence. Many studies rely on relatively small samples—as few as nine participants per group in the musculoskeletal research [12], fewer than 100 participants in the depression and inflammatory-marker studies [6, 17]—limiting statistical power and generalizability. Landmark cohort data, while large and long-running, often reflect hormonal formulations no longer in common clinical use, complicating direct application to current prescribing [8]. Cross-sectional and survey-based studies are vulnerable to recall and

self-report bias, particularly for subjective outcomes such as perceived weight gain or quality of life [13, 15]. Because "oral contraceptives" encompass a genuinely heterogeneous set of products, studies that do not stratify by progestin type or generation risk averaging together formulations with materially different risk–benefit profiles, a limitation that likely explains at least part of the inconsistency observed in the cognitive and mood literatures specifically.

Clinical and Research Implications

Collectively, this evidence supports a shift away from treating oral contraceptive pills as a single undifferentiated exposure and toward individualized, formulation-aware prescribing and counselling. Clinicians selecting a formulation for a given patient may reasonably weigh progestin-specific thrombotic risk, therapeutic goals such as antiandrogenic benefit in PCOS, and patient-specific vulnerability to weight- or mood-related side effects, particularly among patients with elevated BMI. For researchers, priority areas include larger, prospective, progestin-stratified studies of cognitive and mood outcomes; updated mortality and cardiovascular data reflecting contemporary low-dose formulations; and expanded geographic representation—particularly in Southeast Asia, the Pacific, and other underrepresented regions—so that emerging contraceptive technologies such as on-demand pericoital pills are evaluated across diverse populations before wider rollout.

CONCLUSION

Across seventeen recent publications spanning historical review, mechanistic physiology, randomized and cohort studies, and patient-reported outcome research, oral contraceptive pills emerge as a pharmacologically diverse class whose effects cannot be summarized by a single risk–benefit statement. Cognitive, cardiovascular, metabolic, musculoskeletal, and psychological findings each depend substantially on formulation-specific factors—particularly progestin type and generation—rather than on oral contraceptive use as an undifferentiated exposure. Several of the more alarming historical safety signals, including elevated all-cause mortality and clinically significant depression risk, are not strongly supported by more recent or better-controlled evidence, particularly for lower-dose contemporary formulations. At the same time, well-established formulation-dependent risks, such as differential venous thromboembolism risk by progestin type, and persistent tolerability concerns—especially weight-related discontinuation among higher-BMI users—remain important considerations for clinical counseling and future product development. As new formulations such as on-demand pericoital pills move toward wider use, and as the evidence base continues to mature, individualized, progestin-informed prescribing, supported by research that stratifies rather than aggregates across formulations,

represents the most promising path toward optimizing both the safety and the patient-centered acceptability of oral contraceptive pills.

REFERENCES

1. Warren AM, Gurvich C, Worsley R, Kulkarni J. A systematic review of the impact of oral contraceptives on cognition. *Contraception*. 2014 Aug 1;90(2):111-6.
2. Dhont M. History of oral contraception. *The European Journal of Contraception & Reproductive Health Care*. 2010 Dec 1;15(sup2): S12-8.
3. Sun H, Sivasubramanian R, Vaidya S, Barve A, Jarugula V. Drug-drug interaction studies with oral contraceptives: pharmacokinetic/pharmacodynamic and study design considerations. *The Journal of Clinical Pharmacology*. 2020 Dec;60: S49-62.
4. Glasier A, Edelman A, Creinin MD, Han L, Matulich MC, Brache V, Westhoff CL, Hemon A. Mechanism of action of norgestrel 0.075 mg a progestogen-only pill. I. Effect on ovarian activity. *Contraception*. 2022 Aug 1; 112:37-42.
5. Bell S, Gibbs S, Winskell A, Villarino X, Gill H, Little K. Acceptability of an on-demand pericoital oral contraceptive pill: a systematic scoping review. *Reproductive Health*. 2024 Jun 28;21(1):93.
6. Ramzi F, Althanoon ZA, Merkhani MM. Hemoinflammasome Potential of Oral Contraceptive Pills in Women at Child-Bearing Age. *Bahrain Medical Bulletin*. 2024 Jun 1;46(2).
7. Fruzzetti F, Di Carlo C, Bruni V, Cagnacci A. Combined oral contraceptive prescription patterns for therapeutic purposes: results from a subanalysis of the multinational PRO-E2 study. *The European J Contraception & Reproductive Health Care*. 2025 Jul 4;30(4):170-6.
8. Charlton BM, Rich-Edwards JW, Colditz GA, Missmer SA, Rosner BA, Hankinson SE, Speizer FE, Michels KB. Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study. *BMJ*. 2014 Oct 31;349.
9. Shukla AK. Adverse effect of combined oral contraceptive pills. *Asian Journal of Pharmaceutical and Clinical Research*. 2016 Jan 1.
10. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecology and Obstetrics*. 2018 Feb 22;141(3):287.

11. Farris M, Bastianelli C, Habiba M, Benagiano G. Hormonal contraception, past, present, and future part 2: optimizing combined oral contraceptives to decrease risks for healthy women. *Expert Review of Clinical Pharmacology*. 2025 Jun 3;18(6):361-72.
12. Hicks KM, Onambélé-Pearson G, Winwood K, Morse CI. Oral contraceptive pill use and the susceptibility to markers of exercise-induced muscle damage. *European J Applied Physiology*. 2017 Jul;117(7):1393-402.
13. Maiti M, Madhu NR. Effects of oral contraceptive pill on female health. *IAPH*. 2022 Jan 1.
14. Forslund M, Melin J, Alesi S, Piltonen T, Romualdi D, Tay CT, Witchel S, Pena A, Mousa A, Teede H. Different kinds of oral contraceptive pills in polycystic ovary syndrome: a systematic review and meta-analysis. *European J Endocrinology*. 2023 Jul;189(1): S1-6.
15. Zaman A, Strawderman M, Groth SW, Lohse B, Vitek W, Thorpe Jr RJ, Heitman E. Current Body Mass Index Is Associated with Reported Weight Gain as a Reason for Discontinuing Oral Contraceptive Pill Use. *Obesities*. 2026 Mar 29;6(2):20.
16. Coussa A, Hasan HA, Barber TM. Impact of contraception and IVF hormones on metabolic, endocrine, and inflammatory status. *J Assisted Reproduction and Genetics*. 2020 Jun;37(6):1267-72.
17. Comparative cross-sectional study of depression prevalence among Thai women with polycystic ovary syndrome (PCOS): 48 combined oral contraceptive users vs. 48 non-users.

