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Review Article

Impact of hormonal contraceptives and hormone replacement therapy on gastrointestinal health: a comprehensive review

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ABSTRACT

Hormonal contraceptives and hormone replacement therapy (HRT) are widely used worldwide. While benefits are well established, exogenous hormones can affect the gastrointestinal (GI) system. These complications often nonspecific and delayed are underrecognized. In this review, we surveyed PubMed/MEDLINE/Embase through September 2025, assessing hormonal contraceptives or HRT in relation to GI/hepatobiliary outcomes. It was found that estrogen-containing contraceptives are most strongly linked to hepatocellular adenoma (HCA), with dose–duration dependence; lesions typically stabilize or regress after hormone withdrawal. Focal nodular hyperplasia showas no causal relationship and usually does not require contraceptive cessation once confidently diagnosed. Estrogen-induced cholestasis reflects down-regulation of canalicular transporters (e.g., BSEP, MRP2) and is more likely in genetically predisposed women, such as those with prior cholestasis of pregnancy. Estrogen increases biliary cholesterol; progestins reduce gallbladder contractility, together promoting lithogenesis – This effect is stronger with HRT than low dose combined contraceptives. Estrogen-associated pancreatitis occurs primarily via severe hypertriglyceridemia and is amplified by familial dyslipidemias, diabetes, or metabolic syndrome. Hormonal agents modulate motility and visceral sensitivity, contributing to nausea, bloating, and early satiety; symptom fluctuations may be greater with hormone-free intervals. Epidemiology consistently links combined oral contraceptives to Crohn's disease in a dose- and duration-dependent fashion. Long-term hormonal therapy can influence GI health via hepatic, lipid, immune, and motility pathways. Absolute risks are low for most users, but individualized counselling, shared decision-making, and targeted monitoring improve safety while preserving therapeutic benefits. Further mechanistic and longitudinal studies are needed to refine risk stratification.

Keywords: Hormonal contraceptives, Hormone replacement therapy, Gastrointestinal complications, Hepatobiliary disorders, Estrogen-induced cholestasis, Hepatocellular adenoma

INTRODUCTION

Nearly 300 million women globally use hormonal contraceptives, and approximately 20 million women worldwide use hormone replacement therapy.[1,2] Although considered safe, effective, and reversible in women without contraindications, studies have revealed significant adverse with hormonal medication use, including cancer, cardiovascular, gastrointestinal, and metabolic complications.[1] Amongst these, gastrointestinal complications are underreported and underrecognized, owing to the non-specificity of symptoms like nausea and bloating, onset associated with long-term use, and the rarity of manifestations like gastrointestinal tumors, pancreatic disease, and inflammatory bowel disease.[3] This under-recognition potentially conceals the burden of these complications impacting users' quality of life in addition to their reproductive and overall health. Added to that, the widespread use of these medications across the world underscores the need to address potential limitations.

Despite this, there is a scarcity of literature on the topic, and the relationship between hormonal therapies and gastrointestinal health is not fully understood.

In this review, we aim to consolidate the current evidence on gastrointestinal complications associated with hormonal medication in women. We attempt to provide an overview of different hormonal formulations, to explore the spectrum of GI complications and their pathogenic mechanisms, and to identify existing gaps and scope for future research. In doing so, we hope to aid physicians in understanding and improving GI outcomes in reproductive-age patients with contraceptive needs and in postmenopausal women requiring hormonal replacement. Figure 1 can be referred for the key mechanisms of estrogen induced gastrointestinal complications.

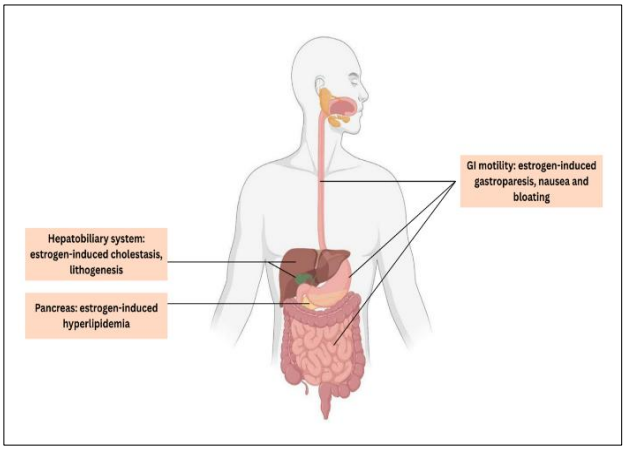

Figure 1: Key mechanisms of estrogen-induced gastrointestinal complications.

OVERVIEW

Types of hormonal contraceptives

Hormonal contraceptives are available in different dosage and delivery forms include oral preparations, injectables, subdermal implants, intravaginal rings, and intrauterine contraceptive devices (IUCDs). Of these, oral contraceptive pills are the most commonly used form in developed countries, and the third most common in developing countries.[4]

Hormonal compositions

Most contraceptives have varying ratios of estrogens and progestins or may contain only progestins. Oral contraceptives with a combination of estrogen and progestins are known as combined oral contraceptive pills (COCPs), whereas the progestin only formulations are progestin only pills (POPs). While estrogen is available in its natural form, or as ethinylestradiol (EE), progestins are available in multiple formulations including levonorgestrel, GSD, desogestrel and etonogestrel. Over the years, doses of EE were reduced because of the side effects associated with a high estrogenic state. Now pills are available with doses as low as 35, 30, 20, 15 and 10 µg.[4] Injectable progestins like depot medroxyprogesterone acetate (DMPA) and norethindrone enanthate, subdermal implants like Implanon and Norplant, and levonorgestrel intrauterine devices are effective progestin only preparations.

Hormone replacement therapy

Oral estrogen, parenteral estrogen and combined estrogen and progestogen preparations are used for hormonal replacement in post-menopausal women. Conjugated equine estrogen is the most commonly form of oral estrogen. Many of these estrogens are metabolized in the liver and have pronounced hepatic effects. Parenteral estrogen on the contrary, bypasses first-pass metabolism in the liver. Combination therapy is preferred to avoid unopposed estrogenic side effects, however dosages should be determined on an individual basis based on hysterectomy status and comorbidities.[5] Figure 2 shows a detailed classification of hormonal medications.

HEPATOBILIARY COMPLICATIONS

Hepatic adenomas

Hepatocellular adenoma (HCA) is the canonical hepatobiliary complication linked to estrogen exposure from combined oral contraceptives (COCs). Although uncommon, HCAs matter clinically because of risks of hemorrhage and malignant transformation. The association appears dose- and duration-dependent, reflecting historical experience with higher-dose pills and contemporary observational series.[6,7] Crucially, tumor behavior improves after hormone withdrawal: in a cohort study, 98% of HCAs stabilized or regressed after cessation of COCs, with no HCA-related complications during follow-up.[8]

Current reviews estimate hemorrhage in a substantial minority of cases (more likely when lesions are >5 cm, subcapsular, or during pregnancy) and a low but real risk of malignant transformation, enriched in β-catenin–activated subtypes and in male patients.[6,7] Accordingly, guidance favors conservative management (stop estrogen, monitor with MRI) for women with small, asymptomatic lesions, reserving resection for >5 cm, growth despite withdrawal, symptomatic tumors, or any HCA in men.[6,7,9]

Evidence tying progestin-only methods (POPs, depot medroxyprogesterone, implants, levonorgestrel-IUD) to HCA is limited and far less consistent than for estrogen; when HCAs are identified, clinicians typically discontinue exogenous estrogen first and individualize decisions on progestin-only continuation while monitoring radiologic response.[6,9]

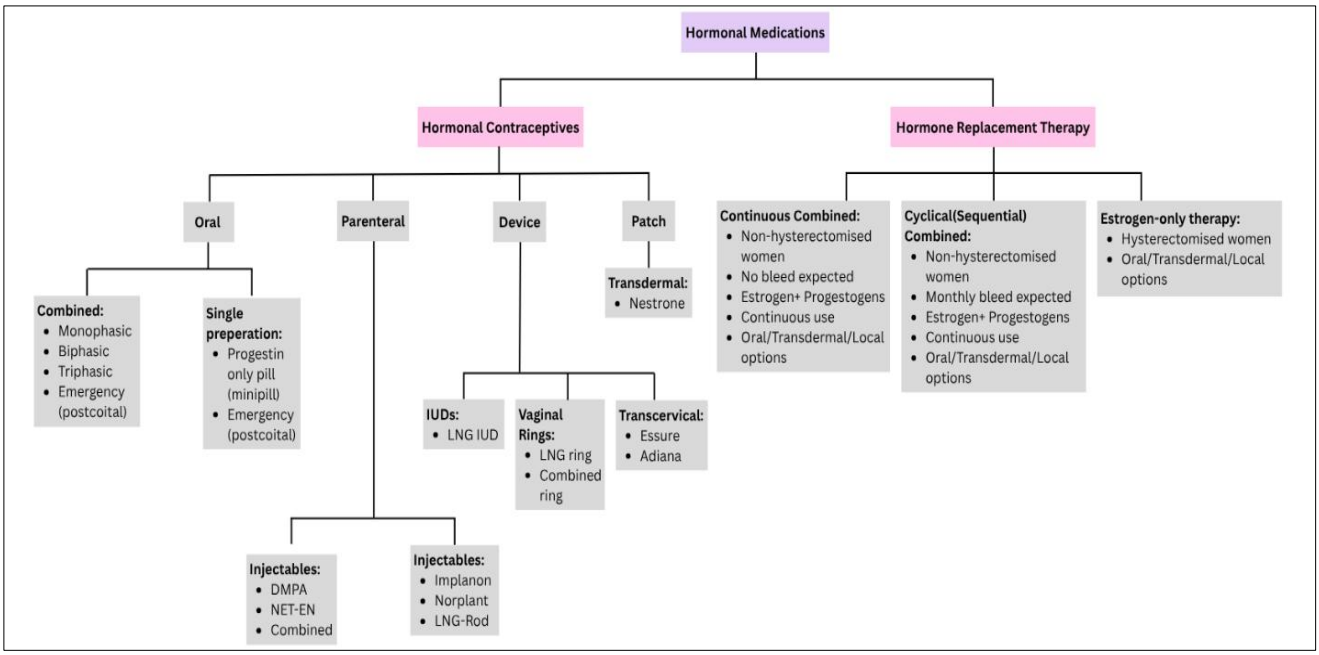

Figure 2: Classification of hormonal medications.

Focal nodular hyperplasia (FNH)

FNH is a benign hyperplastic response to vascular anomalies and represents an important differential diagnosis. Modern series do not support a causal link between COCs and the development of FNH, although occasional growth under high-estrogen states has been described.[7] Imaging usually distinguishes FNH from HCA (e.g., central scar and hepatobiliary contrast uptake in FNH; fat, hemorrhage, and lack of scar in many HCAs), sparing patients with FNH from unnecessary surgery.[7] Because FNH has no hemorrhagic or malignant potential, routine discontinuation of contraception is not required once the diagnosis is secure.[7]

Estrogen-induced cholestasis

Estrogenic contraceptives can precipitate intrahepatic cholestasis in susceptible women, typically within months of initiation and presenting with pruritus, cholestatic liver tests (↑alkaline phosphatase, ±bilirubin), and bland canalicular cholestasis on histology. The pathogenesis is well defined: estrogen-ER signaling perturbs bile acid homeostasis, down-regulates the bile salt export pump (BSEP/ABCB11) and MRP2, suppresses FXR-mediated transcriptional programs, and promotes internalization of canalicular transporters, decreasing bile flow and favoring intrahepatic accumulation of hydrophobic, hepatotoxic bile acids.[10] Most cases resolve after stopping estrogen; supportive therapy (e.g., ursodeoxycholic acid) may be used for pruritus.[10] Genetic predisposition is key: women with a history of intrahepatic cholestasis of pregnancy (ICP) or benign recurrent intrahepatic cholestasis (BRIC) related to variants in ABCB11/ABCB4/ATP8B1 are at heightened risk of contraceptive-triggered cholestasis, and high-dose estrogen should be avoided; progestin-only options are often preferred in these settings.[10]

GALLBLADDER DISEASE

Mechanisms: estrogen, progestins, and biliary physiology

Cholesterol gallstone pathogenesis is strongly influenced by sex hormones. Estrogen increases hepatic cholesterol synthesis and secretion into bile while reducing bile acid synthesis, generating cholesterol-supersaturated (lithogenic) bile. Progestins reduce gallbladder smooth-muscle contractility and slow emptying, promoting stasis. The combination—supersaturation plus stasis—creates a milieu favoring nucleation of cholesterol crystals and stone growth, paralleling physiologic changes of pregnancy.[11,12]

Epidemiology across contraceptive formulations

Historically, higher-dose COCs were associated with gallstones; contemporary evidence with modern low-dose contraceptives shows at most a small risk signal. A 2017 systematic review and meta-analysis (>550,000 women) found no statistically significant increase in cholelithiasis with oral contraceptive use overall (pooled RR≈1.19, 95% CI 0.97–1.45), whereas menopausal hormone therapy (HRT) was associated with a markedly higher risk (RR≈1.79).[13] These findings suggest that the estrogen dose, exposure duration, and hepatic first-pass effects seen with HRT in older women are more gallstone-relevant than contemporary contraceptive doses.

Population-level trends also matter: a 2024 global synthesis shows rising gallstone prevalence driven

predominantly by obesity, metabolic syndrome, and aging, factors that dwarf any modest contraceptive contribution.[12] Data specific to progestin-only pills, injectables, implants, and levonorgestrel IUDs are comparatively sparse; where studied, risks appear low and difficult to disentangle from confounding by indication and background metabolic risk.[11,12] Overall, for most reproductive-age users, absolute risk increases—if any—are small, and modern contraceptives are unlikely to be a major driver of gallstone disease.[11–13]

Risk modifiers and clinical implications

Gallstone risk is multifactorial: female sex, age, BMI/obesity, rapid weight loss, dyslipidemia/insulin resistance, and genetics (e.g., ABCG8 variants) are dominant determinants.[11,12] In an obese patient with a strong family history, even a small estrogen-related lithogenic effect could become clinically relevant; for a lean patient with few risk factors, modern COC exposure likely confers minimal excess risk. Clinically, outcomes among contraceptive users mirror the general population: biliary colic, cholecystitis, choledocholithiasis, and gallstone pancreatitis occur at usual frequencies, and standard management applies. HRT in postmenopausal women remains a clearer gallstone risk than COCs; if hormone therapy is needed in older women with gallstone risk, non-oral routes (to reduce hepatic first-pass) are often considered, though this principle has been studied mainly in HRT rather than contraceptive dosing.[11]

Practical approach

For hepatobiliary safety in contraception counselling - suspected/known HCA: stop estrogen; consider progestin-only or non-hormonal methods; resect if >5 cm, growing, symptomatic, or β-catenin–activated/male, FNH: distinguish confidently from HCA; if FNH, no routine change in contraception is required , history of ICP/BRIC or prior estrogen cholestasis: avoid high-dose estrogen; prefer progestin-only or non-hormonal options, gallstones/gallbladder disease risk: emphasize weight control and metabolic risk reduction; modern COCs contribute minimally compared with obesity and age.[6,7,9-11,13]

PANCREATIC COMPLICATIONS

There are two main mechanisms hypothesized for estrogen induced acute pancreatitis – The first is the development of hypertriglyceridemia as an independent event or the unmasking of an underlying familial hyperlipoproteinemia. The second mechanism is the formation of a hypercoagulable state secondary to estrogen, which can lead to pancreatic necrosis.[14] In the majority of patients hypertriglyceridemia is the central mechanism, with a critical step being the hydrolysis of triglycerides by pancreatic lipase and accumulation of free fatty acids in the pancreas.[14–17] In 1973, Davidoff et al documented patient reports of severe hypertriglyceridemia secondary to the use of a variety of estrogen therapy. They developed a rare pattern of hypertriglyceridemia in the absence of chylomicrons (type 4 pattern hyperlipidemia). Avoidance of estrogenic therapy is advised in patients with more common familial hyperlipidemias (type 1 and type 5) which show chylomicrons, as well as type 4 hyperlipidemias. Caution is also warranted in patients with diabetes, hyperlipidemia, atherosclerosis and other comorbidities. In addition, administration of pregestational agents alone to women with type 5 hyperlipidemia has been reported to significantly improve lipid abnormalities.[15] Some of the proposed management strategies for hypertriglyceridemia in the setting of acute pancreatitis include insulin and heparin infusions which stimulate lipoprotein lipase, as well as plasma exchange to rapidly reduce triglyceride levels.[18] In a large prospective study conducted in Sweden in 2014, the association of postmenopausal hormone replacement therapy and acute pancreatitis was studied. The relative risk of acute pancreatitis between ever users of hormone replacement therapy and never users was found to be significant (RR 1.57, 95% CI 1.20-2.05). No difference was found between current or past use of HRT, but risk was higher among women with duration of therapy of more than 10 years, as well as among women using systemic therapy.[16] Further studies are needed to define optimal screening recommendations and management strategies.

GI MOTILITY AND FUNCTIONAL DISORDERS

While there is little evidence to support the effects of normal cyclical hormonal fluctuations on gastric motility, several animal models support the notion that exogenous estrogen delays gastric emptying through various mechanisms. Some of them include induction of nitric oxide release from non-adrenergic, non-cholinergic nerves of the gastrointestinal tract, cholecystokinin stimulation via cholecystokinin (A) receptor, and vagal-mediated nociceptive changes.[19] Although oral contraceptive use promotes lithogenesis by increasing cholesterol concentration in bile, a decrease in gallbladder emptying was not observed on direct ultrasonographic comparison of gallbladder kinetics. Against this, hormone replacement therapy is associated with an increased incidence of gallbladder disease, warranting avoidance of HRT in women with asymptomatic cholelithiasis.[19]

Hormonal contraceptives are associated with nausea, bloating, belching, early satiety and fullness. A recent study showed that premenopausal women using hormonal contraceptives were found to have significantly more frequent and severe nausea and bloating compared to non-users, postmenopausal women and men, especially when allowing a hormone-free interval between contraceptive use compared to continuous use. It is hypothesized that the hormone-free intervals lead to greater fluctuation in serum estrogen and progesterone levels, which can exacerbate nausea in patients by their action on the chemoreceptor trigger zone.[20]

Through its action on visceral pain sensation, estrogen has been implicated in the pathophysiology of the chronic pain associated with irritable bowel syndrome (IBS) and is more commonly observed in premenopausal women compared to men. Thus, adoption of a gender-specific treatment plan is advisable.[19,21]

INFLAMMATORY BOWEL DISEASE (IBD) RISK

Epidemiological studies have consistently linked combined oral contraceptives (COCPs) with an increased risk of inflammatory bowel disease, particularly Crohn's disease (CD). A large nested case–control study using UK primary care data found that COCP use was associated with a 60% increased risk of CD (OR 1.60, 95% CI 1.41–1.82), with the highest risk observed among current users of second-generation COCPs (OR 2.12, 95% CI 1.83–2.44).[22] The association demonstrated a dose–response pattern, with each additional month of COCP exposure per year conferring a 6.4% increase in CD risk and each incremental microgram per day of ethinylestradiol increasing risk by 3.1%. In contrast, progestin-only pills (POPs) and parenteral methods were not associated with CD. Ulcerative colitis (UC) demonstrated weaker but still significant associations, with odds ratios between 1.25 and 1.38 for current COCP and POP use, alongside a modest 3.3% increase in risk per month of COCP exposure. Interestingly, UC risk was slightly higher among non-smokers using COCPs compared to smokers, suggesting potential effect modification by lifestyle factors.[22]

Interpretation of these associations must account for potential confounders. Smoking is a particularly strong modifier of IBD risk, independently increasing the likelihood of Crohn's disease while exerting a protective effect in UC. Several studies suggest OCPs and smoking may act synergistically in CD, although others have found no significant interaction.[23,24] Lifestyle and socioeconomic factors may also contribute, as women using OCPs differ from non-users in diet, healthcare utilization, and reproductive history.[23] Recall bias in self-reported contraceptive use has limited prior studies, but designs incorporating electronic prescribing records mitigate this concern.[25] Genetic predisposition may further shape risk, as loci such as NOD2, ATG16L1, and IRGM1 regulate immune responses and barrier integrity.[26] Taken together, while high-quality studies strengthen the case for an independent effect of OCPs, residual confounding cannot be fully excluded.

Although the epidemiological signal is compelling, the precise biological mechanisms remain incompletely understood. Experimental data suggest that exogenous estrogen may impair intestinal barrier function and modulate mucosal immunity, particularly in genetically predisposed individuals.[27] Several Crohn's disease susceptibility genes, such as IRGM1, ATG16L1, NOD2, PTPN2, and PRDM1, regulate innate immune signalling and epithelial integrity, raising the possibility of gene–environment interactions with hormonal exposure.[27] Oral contraceptives also alter endogenous sex hormone balance, increasing circulating estrogen and sex hormone–binding globulin while reducing testosterone and dehydroepiandrosterone sulfate.[27] Testosterone has been shown to suppress innate immune activation, including Toll-like receptor 4–mediated pathways; thus, its reduction may contribute to a pro-inflammatory state.[27] In addition, hormonal contraceptives have been linked to changes in microbial communities, and animal studies suggest bidirectional interactions between gut commensals, endogenous testosterone levels, and autoimmune susceptibility.[27] Other proposed mechanisms include microvascular ischemia induced by hormonal contraceptives, which could facilitate focal intestinal injury. Divergent effects on CD and UC may also reflect their distinct cytokine profiles, with Crohn's inflammation driven predominantly by Th1 pathways and UC by Th2 pathways, the latter more strongly influenced by estrogen.[27]

Taken together, these findings indicate that oral estrogen exposure is the primary driver of IBD risk, particularly Crohn's disease, in a duration- and dose-dependent fashion. POPs and parenteral methods appear to have a more favorable safety profile, offering potentially safer alternatives for women at elevated baseline risk of IBD.

MALIGNANCY RISK

Colorectal cancer

The relationship between oral contraceptive (OC) use and colorectal cancer (CRC) has been examined extensively, with most studies suggesting a modest protective effect. A meta-analysis of eight case–control and four cohort studies reported a pooled relative risk (RR) of 0.82 (95% CI: 0.74–0.92) for ever-users compared with never-users.[28] Stratified analyses showed consistent reductions across designs: case–control studies (RR 0.72, 95% CI: 0.61–0.85) and cohort studies (RR 0.84, 95% CI: 0.72–0.97). Protective associations were observed for both colon (RR 0.83, 95% CI: 0.74–0.95) and rectal cancers (RR 0.74, 95% CI: 0.59–0.93). Duration of use did not demonstrate a clear dose–response, although limited evidence suggested a stronger effect among more recent users (RR 0.46, 95% CI: 0.30–0.71).[28]

By contrast, data from the Nurses' Health Studies (NHS I and II), two of the largest prospective cohorts with over 180,000 women and 5 million person-years of follow-up, did not confirm a consistent protective association. In NHS I, ever-use of OCs was not associated with CRC (RR 1.01, 95% CI: 0.91–1.12), nor was any subsite-specific risk significantly altered.[29] Similarly, NHS II reported null overall findings (RR 1.03, 95% CI: 0.69–1.53). However, a potential signal was observed for long-term users: women with ≥5 years of OC use demonstrated a lower risk of colon cancer (p=0.02). Importantly, associations did not vary by age, BMI, smoking, alcohol consumption,

physical activity, folate intake, or family history, reducing the likelihood of major confounding.[29]

Taken together, evidence suggests that oral contraceptive use may modestly reduce CRC risk, particularly with longer or more recent use, but large prospective data raise the possibility that this protective effect is less pronounced than early studies implied. Proposed mechanisms include estrogen-mediated modulation of bile acid metabolism, reduction of carcinogenic secondary bile acids, and systemic anti-inflammatory effects that may mitigate colonic epithelial injury and neoplastic progression.

Liver cancer

The association between oral contraceptive use and primary liver cancer (PLC) has been debated for decades. Early case–control studies suggested increased risk, but were limited by small sample sizes, recall bias, and inadequate adjustment for hepatitis B/C or alcohol. An updated meta-analysis of 17 epidemiological studies reported no significant association between ever-use of OCs and PLC risk, in contrast to earlier positive findings.[30] This reinforces the likelihood that previously reported associations were due to bias or confounding, and that modern low-dose OC formulations are unlikely to confer substantial hepatocarcinogenic risk. In contrast, menopausal hormone therapy (MHT) was linked to a reduced risk of PLC, though formulation-specific effects remain uncertain. Experimental evidence supports a potential protective role for estrogen and progesterone signaling in hepatocarcinogenesis.[30] Overall, while OCs clearly increase the risk of benign hepatic adenomas, current data do not support a causal role in hepatocellular carcinoma, and some evidence suggests MHT may even be protective.[30]

Pancreatic cancer

The relationship between oral contraceptive (OC) use and pancreatic cancer risk remains inconclusive. Large population-based analyses and cohort studies have consistently reported no significant association between ever-use of OCs and pancreatic cancer, regardless of formulation or era of use.[31] By contrast, menopausal hormone therapy (MHT) has shown a more consistent protective effect, particularly with estrogen-only regimens, which were associated with up to a 70–80% reduction in risk after adjustment for major confounders including smoking, alcohol, and body mass index.[31]

Beyond exogenous hormone exposure, sex differences in pancreatic cancer incidence further support a potential hormonal influence.[32] Men have a consistently higher risk of pancreatic cancer than women, a disparity not fully explained by established risk factors. Reproductive factors such as prolonged breastfeeding have also been identified as protective, suggesting that cumulative lifetime exposure to endogenous or exogenous estrogens may contribute to risk modulation.[32] Taken together, these findings reinforce the hypothesis that sex hormones influence pancreatic carcinogenesis, though their protective effects appear more evident in the postmenopausal setting with hormone therapy than in premenopausal women using contraceptives. Further pooled analyses, stratified by menopausal status and hormone formulation, are warranted to clarify the role of hormonal exposures in pancreatic cancer prevention.

SPECIAL POPULATIONS AND GENETIC RISK

Pre-existing liver disease

Careful risk stratification is necessary for women with liver illness. Because of their increased risk of cholestatic damage and decreased metabolism of estrogen, combined hormonal contraceptives (CHCs) are contraindicated in decompensated cirrhosis but are deemed appropriate in compensated cirrhosis. CHCs are categorized as category 1 (no restriction) for compensated cirrhosis and category 4 (unacceptable health risk) for decompensated cirrhosis by the American Association for the Study of Liver Diseases and the U.S. Medical Eligibility Criteria for Contraceptive Use.[33,34] Because estrogens encourage the growth of adenomas and raise the risk of bleeding or malignant transformation, CHCs are contraindicated in women with hepatic adenomas; progestin-only techniques are recommended in these situations.[35] For focal nodular hyperplasia, CHCs are generally regarded as category 2 (advantages generally outweigh risks), as lesion size and number are not changed by hormonal contraceptive use. All hormone treatments are category 4 and should be avoided in women with malignant liver tumors. Because of the high risk of recurrence and potential for serious liver damage, estrogen-containing contraceptives are also contraindicated in women with cholestatic diseases, such as a history of pregnancy-related cholestasis or benign intrahepatic recurrent cholestasis. For all high-risk liver disorders, progestin-only or non-hormonal approaches are recommended.[33-37]

Familial hyperlipidemia

Because estrogen raises serum triglyceride levels and hepatic VLDL synthesis, women with severe hypertriglyceridemia or familial hyperlipidemia are more likely to develop acute pancreatitis when using estrogen-containing contraceptives. Women with severe hypertriglyceridemia should refrain from using estrogen-based treatments, according to the National Lipid Association, which also suggests baseline and recurring lipid monitoring for women with a history of extremely high LDL-C or triglycerides. In these groups, progestin-only or non-hormonal approaches—like intrauterine devices or subdermal implants—are recommended.[38]

Hereditary thrombophilia

Conditions like prothrombin mutation, protein C/S deficiency, factor V Leiden, and prothrombin G20210A

mutation increase the risk of venous thromboembolism (VTE) approximately sixfold. The absolute risk of VTE is higher in individuals with severe thrombophilia compared to those with mild or moderate forms.

Personal/family history of IBD

The use of combined oral contraceptives is linked to a slightly elevated risk of Crohn's disease, with the risk rising with prolonged exposure. Parenteral progestin-only contraception is not linked to ulcerative colitis or Crohn's disease, and progestin-only tablets are not associated with an increased risk of Crohn's disease. Progestin-only or non-hormonal approaches are recommended for women with a personal or family history of IBD, particularly Crohn's disease, in order to reduce risk.[34]

Cholestasis of pregnancy

Using estrogen-containing contraceptives increases the risk of cholestasis recurrence in women with a personal or family history of intrahepatic cholestasis or pregnancy cholestasis. Progestin-only or non-hormonal approaches are recommended for these women instead of estrogen-containing contraceptives, according to U.S. MEC and hepatology guidelines.[35,39]

Pharmacogenomic factors

The hepatic cytochrome P450 pathway is used to metabolize hormonal contraceptives. The effectiveness and safety of contraceptives can be altered by genetic variations in CYP450 enzymes and drug-drug interactions, particularly with antiretrovirals, anticonvulsants, and some antibiotics. Referrals to complex family planning specialists are advised in complicated circumstances. Women on interfering drugs or with known pharmacogenomic risk factors prefer progestin-only treatments, especially levonorgestrel intrauterine devices, which are less susceptible to CYP450-mediated interactions.[40]

In conclusion, estrogen-containing contraceptives should be avoided by women who have a history of cholestasis during pregnancy, hepatic adenomas, malignant liver tumors, cholestatic diseases, severe hypertriglyceridemia, or decompensated liver disease. In these high-risk groups, progestin-only or non-hormonal approaches are recommended, with customized risk assessment and continuous monitoring as needed.[40]

CLINICAL RECOMMENDATIONS AND MONITORING

Risk assessment prior to initiation

Check for a family history of inflammatory bowel disease (IBD), hyperlipidemia/hypertriglyceridemia, and liver illness (including cirrhosis, hepatic adenoma, focal nodular hyperplasia, and cholestasis of pregnancy) and determine other risk factors that may interact with hormonal contraceptives, such as obesity, metabolic syndrome, and concomitant drugs (particularly those that impact CYP450 metabolism).[34,40]

Standard laboratory monitoring

Liver function tests (LFTs)

Before beginning estrogen-containing contraceptives, women with a history or risk of liver disease should have baseline LFTs. For those with persistent risk or symptoms suggesting hepatic dysfunction, periodic monitoring is recommended.[34,35]

Lipid profiles

Women with known or suspected familial hyperlipidemia or hypertriglyceridemia should have baseline and periodic lipid panels, particularly if they are considering estrogen-containing methods.[38]

IBD assessment

Women with a personal or family history of IBD should consider non-estrogen choices and monitor for any new or worsening gastrointestinal symptoms.[34]

Choosing contraceptives for high-risk populations

Pre-existing liver disease

Avoid estrogen-containing birth control in malignant liver tumors, hepatic adenomas, decompensated cirrhosis, or history of pregnancy-related cholestasis. Non-hormonal or progestin-only approaches are recommended.[34,35,37]

Familial hyperlipidemia/hypertriglyceridemia

Avoid estrogen-containing birth control in extreme cases because of the risk of pancreatitis. Non-hormonal or progestin-only approaches are recommended.[38]

Individual or family history of IBD

Prefer non-hormonal or progestin-only approaches, particularly for those at risk for Crohn’s disease.[34]

Pregnancy cholestasis

Avoid estrogen-containing contraceptives because of the increased risk of recurrence.[35,39]

Shared decision-making and patient counselling

Discuss the trade-off between gastrointestinal risks and the benefits of contraception. Educate patients on warning signs such as jaundice, severe abdominal pain, and new gastrointestinal symptoms. Encourage timely symptom

reporting and consistent monitoring.[40] Figure 3 may be referred for clinical recommendations.

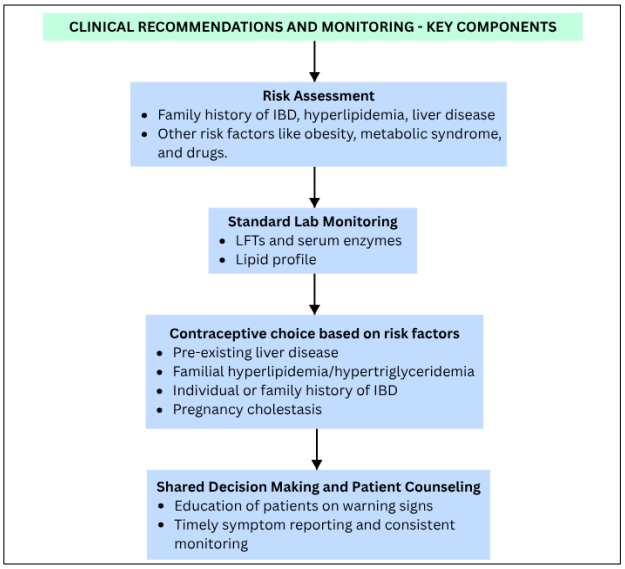

Figure 3: Clinical recommendations and monitoring.

CONCLUSION

The aim of this study is to highlight the importance of recognizing gastrointestinal side effects associated with long-term hormonal therapy, an area which remains underrecognized. Long-term hormonal therapy can influence GI health via hepatic, lipid, immune, and motility pathways. Absolute risks are low for most users, but individualized counselling and targeted monitoring improve safety while preserving therapeutic benefits. Further mechanistic and longitudinal studies are needed to refine risk stratification and advancing personalized hormonal care.

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