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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Non-Contraceptive Benefits of Hormonal Contraception: Established Benefits and New Findings

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Abstract
Purpose of Review The majority of women who use contraception acknowledge the non-contraceptive benefits and many women use contraception solely for these benefits. The purpose of this review is to discuss the established benefits and highlight recent advances in our understanding of non-contraceptive benefits.
Recent Findings Combined hormonal contraception (CHC), especially extended-cycle CHC, provides significant improvement for women suffering from heavy menstrual bleeding, pelvic pain, menstrual migraines, and mood disorders. The levonorgestrel intrauterine device (LNG IUD) provides improvement in pain and bleeding beyond that of CHC although its effectiveness may be mediated by pre-existing bleeding patterns. CHC and LNG IUD are protective against gynecologic cancers and data continues to emerge on non-gynecologic cancer risk. Hyperandrogenism is best treated with CHC containing newer progestins. LNG IUD may be used in the treatment of endometrial hyperplasia or carcinoma and is effective for endometrial protection during estrogen replacement. CHCs promote healthy vaginal flora.
Summary Counseling on contraception should include a discussion of both the risks and benefits. In most women, the benefits are substantial and outweigh the risks.

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Introduction

From its inception, hormonal contraception has been used to treat heavy menstrual bleeding and dysmenorrhea. The first hormonal birth control, an oral method of combined hormonal contraception (CHC), was initially approved in 1957 by the Food and Drug Administration (FDA) for the treatment of menstrual disorders [1]. It took 3 years for the FDA to approve it as a contraceptive. Since the 1960s, the list of benefits has steadily expanded. It now includes beneficial effects for non-reproductive aged women as well as for non-gynecologic conditions. Today, 58% of women using contraception cite non-contraceptive benefits as a reason for its use and 14% use it solely for a non-contraceptive indication [2, 3]. Knowledge of non-contraceptive benefits may help both physicians and patients make informed decisions about contraceptive use and lead to improved patient satisfaction and compliance. Through this article, we aim to describe the impact of hormonal contraception on multiple medical conditions and highlight recent advances in the understanding of non-contraceptive benefits.

Heavy Menstrual Bleeding

Clinicians have used various hormonal contraceptive agents to help women control their heavy bleeding for decades. Older studies have shown that CHC use can decrease menstrual blood loss by as much as 50%. The levonorgestrel intrauterine device (LNG IUD) has gained more acceptance and widespread use as a contraceptive

method and studies suggest that it can decrease blood loss by as much as 97% after the first year of use [4]. Although endometrial ablation was found to be slightly better than the LNG IUD for controlling heavy menstrual bleeding (RR 1.19, 95% CI 1.07–1.32), there was no difference in satisfaction rates at 1 and 2 years [5].

A randomized controlled trial (RCT) of medical management versus LNG IUD enrolling 571 women in the UK found that all women had improvements in their heavy menstrual bleeding, with IUD users having significantly better scores on the 100-point menorrhagia multiattribute scale (32.7 vs 21.4 points). LNG IUD users were almost twice as likely to be using the method after 2 years (64 vs 38%) [6••]. A recent retrospective analysis from a large database showed that while women were more likely to use short acting hormonal methods to control heavy bleeding associated with uterine fibroids, those who chose long-acting hormonal methods were less likely to switch treatments or pursue surgery (HR 0.84, 95% CI 0.79–0.91) [7]. A Cochrane database review from 2015 also found that compared to oral medications, the LNG IUD more effectively decreased heavy menstrual bleeding [8].

The beneficial effect of the LNG IUD on menorrhagia has been replicated in younger populations as well as in women with bleeding disorders [9]. A study of 18–25-year-old nulliparous women with regular menses found a subjective decrease in bleeding when using LNG IUD versus CHC (49 vs 22%) [10]. An observational study in New Zealand found that 58% of adolescents who use LNG IUD do so for primary treatment of heavy menstrual bleeding, with a continuation rate of 85% at 1 year, suggesting satisfaction with treatment [11]. LNG IUD is also safe and well accepted by morbidly obese adolescents, as demonstrated by a 92% acceptance rate and a 91% continuation rate at 6 months when inserted at the time of bariatric surgery [12].

One caveat to the use of LNG IUD for treatment of heavy bleeding may be that an individual's response to the method is affected by her pre-existing bleeding pattern. In a recent secondary analysis of women in the Contraceptive CHOICE study who were using the LNG IUD, those who had heavy bleeding prior to insertion were significantly less likely to experience amenorrhea at 1 year of use than women with moderate bleeding (OR 0.36, adjusted 95% CI 0.16–0.69) [13••]. This model adjusted for race and gravidity, which influenced bleeding patterns, with Black women and those with higher gravidity being less likely to report amenorrhea. Jensen et al. reported in 2013 that women with heavy menstrual bleeding were likely to have increased days of bleeding in the first month after insertion, with improved bleeding in each successive month thereafter, achieving an amenorrhea rate of 9% by the end of 1 year [14]. Spotting accounted for about half of the bleeding days.

Pelvic Pain

Dysmenorrhea

In addition to controlling bleeding, hormonal contraception can decrease the dysmenorrhea that many women experience. There is limited evidence from randomized controlled trials [15] but prospective studies and surveys show an improvement in primary dysmenorrhea for women taking oral CHC [4]. Progestin-only methods may be also be effective: a recent non-randomized study of women with dysmenorrhea treated with a daily dose of the progestogen norethisterone produced reductions in pain scores comparable to women treated with a cyclic oral CHC [16]. There is also an increasingly large body of evidence supporting the treatment of pelvic pain with the LNG IUD. A 20-year cohort study of Swedish women reported that use of the LNG IUD or oral CHC was associated with a reduction in the severity of dysmenorrhea compared to those who used non-hormonal methods [17••].

Primary dysmenorrhea in adolescents has a prevalence of 60–93% and causes school absenteeism and interference with daily life [18]. The improvement of dysmenorrhea with CHC and LNG IUD is noted in the adolescent population in multiple observational studies [19••].

Endometriosis

High-quality studies support the use of a LNG IUD in managing secondary dysmenorrhea caused by gynecologic pathology. Cochrane reviews support use of LNG IUD for treatment of endometriosis, both as a primary treatment [20] and post-surgical adjunctive treatment [21]. Shaaban and colleagues randomized 62 women complaining of pain and bleeding thought to be associated with adenomyosis to CHC or LNG IUD [22••]. Both groups had improvements in their pain and bleeding after 6 months. The LNG IUD was more effective, bringing pain scores from 6.23 to 1.68 on a 10-cm visual analog scale (VAS), compared to reductions from 6.5 to 3.9 for the CHC users ($p < 0.001$). The mean number of bleeding days each month decreased from 9.8 to 2.6 for women using the LNG IUD, significantly more than the decrease from 9.9 to 5.2 in the women using CHC ($p < 0.001$). The number of menstrual pads used per day also decreased in both groups, but more for the women using the LNG IUD.

In a 2017 review article, Casper argues that providers should consider oral progestin-only methods for first-line treatment of endometriosis [23]. In contrast to a single RCT comparing CHC with placebo which demonstrated a modest improvement in symptoms at 4 months, there are several RCTs which show that progestin-only treatments, such as depo medroxyprogesterone acetate (DMPA) and norethindrone acetate, are more effective than placebo. These medications also appear to be more effective than CHC in eliminating

pain and reducing visible lesion size on laparoscopy or ultrasound. Norethindrone is FDA-approved for the treatment of endometriosis and the evidence supports doses of 2.5 to 5 mg daily for this indication [23].

Similarly, hormonal contraception may improve endometriosis in adolescents. The first-line therapy for endometriosis in adolescents under 16 years old is continuous CHC for menstrual suppression [24]. The LNG IUD is categorized by the American Congress of Obstetricians and Gynecologists (ACOG) as a second-line treatment for endometriosis [25].

Polycystic Ovarian Syndrome and Hyperandrogenism

CHC has been one of the mainstays of therapy in women with polycystic ovarian syndrome (PCOS). PCOS is thought to be multifactorial in etiology and presents with many different phenotypes and biochemical hallmarks. A systematic review attempted to identify the effects of different hormonal contraception methods on women with varying manifestations of PCOS. In women with hyperandrogenism and PCOS, any CHC method seems to be equally effective at controlling hirsutism and other hyperandrogenic effects. However, hormone formulation or route may impact non-contraceptive benefits among women with obesity, risk for metabolic syndrome, or moderate insulin resistance [26]. A RCT comparing drospirenone-containing CHC to the contraceptive ring found similar effects on blood pressure and lipids, but the ring decreased the area under the curve for glucose, insulin, and C peptide, while the oral regimen increased the insulinogenic index [27]. Another RCT comparing drospirenone-containing CHC to those containing desogestrel found better lipid profile and glycemic profile for the drospirenone-containing oral contraceptives [28].

In a survey of over 2000 patients presenting for an initial visit to dermatology specialists, women reported that vaginal and oral CHC improved acne, while implants, injections, and LNG IUDs worsened acne [29]. No change was noted with different doses of estrogen, whereas a triphasic progestin formulation was beneficial. Additionally, CHC containing third- and fourth-generation progestins improve acne more effectively than first- and second-generation progestins. After a 2012 lawsuit in France changed prescribing habits, a large survey found that 84% of over 800 women changing from a third- or fourth-generation pill to a first- or second-generation pill considered their acne had worsened [30]. Desogestrel, norgestimate, and drospirenone are newer progestins while norethisterone, norgestrel, and levonorgestrel are first- and second-generation progestins.

Menstrual Migraine

Approximately 25% of women experience migraine headaches and of them, more than 50% report an association with their menses [31]. The International Headache Society defines two types of menstrual-associated migraines: the pure *menstrual migraine*, which only occurs with menses, ranging from 2 days prior to menses onset to 3 days after menstrual completion and is without aura; and the *menstrually related migraine*, which occurs at other times of the menstrual cycle and may have an aura [32]. The migraines are believed to occur as estrogen declines in the luteal phase of the menstrual cycle [33, 34]. The goal of hormonal treatment is to eliminate or reduce the estrogen decline that can trigger a headache.

CHC is a first-line preventive therapy and may be associated with up to 80% reduction in frequency and severity of headaches [35]. The hormone-free interval in a standard CHC regimens causes a decline in estrogen that may trigger a migraine; thus, shorter pill-free interval (such as a 24/4 regimen) can improve headache control [36]. Extended and continuous CHC regimens may improve patient satisfaction even further [37–39]. Another alternative includes administering daily estrogen during the placebo week to avoid the estrogen decline, which was associated with 50% fewer days with headache for all participants in a single small study [40]. Additionally, quadriphasic pills which slowly decrease estrogen levels throughout the month are effective in reducing migraine frequency, duration, and intensity ($p < 0.001$) [41]. No studies have evaluated the effectiveness of extremely low-dose estrogen-containing pills (10 μg ethinyl estradiol (EE)).

Progestin-only methods that suppress ovulation may also be beneficial. Two studies of a desogestrel POP that suppresses ovulation decreased the duration of menstrual migraines [42••, 43]. Methods that induce amenorrhea even without inhibiting ovulation (such as the LNG IUD) may also have a beneficial effect on menstrual migraines. In a study of women with a history of menstrual migraine and current contraceptive use, women with amenorrhea (19 women using LNG IUD, 3 using desogestrel POP, 1 using DMPA) reported no migraines in the preceding month [44]. It remains unclear whether norethindrone, the progestin-only pill available in the USA, has a beneficial effect on migraines as it does not consistently suppress ovulation.

Hormonal contraception use in the setting of migraines is not without controversy. Women who have migraines, especially migraines with aura, are at increased risk of stroke. This risk exponentially increases when CHC is used [45]. Because of this risk, CHC is considered Category 4 (unacceptable risk) by the Center for Disease Control (CDC) for women who have migraines with aura but is Category 2 (benefits outweigh the risks) for women who experience migraines without aura [46]. The CDC Medical Eligibility Criteria (MEC) no longer stratifies women with migraine without aura into separate risk

groups based on age. The increased risk of stroke related to CHC is dose-dependent and modern pills containing 30–40 μg ethinyl estradiol increase the risk of stroke less than the original formulations containing over 50 μg EE (OR 1.6 compared to OR 4.5). Use of low-dose CHC, containing 20 μg EE, provides no further risk reduction compared to the 30–40 μg EE pills [47]. The thrombogenic effect of the extremely low-dose10 μg pills is unknown at this time.

Premenstrual Syndrome/PMDD

Sex hormones may also affect mood. Progesterone metabolites act on the gamma-aminobutyric acid (GABA) receptor complex, which is a major inhibitory system in the central nervous system [48], while increasing estrogen levels increase serotonin levels [49, 50]. Premenstrual syndrome (PMS) is characterized by physical or mood symptoms that present in the 5 days prior to the start of menses and end within 4 days of menses that interfere with activities [51]. Premenstrual dysphoric disorder (PMDD), a severe form of PMS, can mimic depression. PMS affects 40% of women, while 5–8% of women experience PMDD [52].

CHC, along with selective serotonin receptor inhibitors (SSRIs), is considered the first-line treatment for PMS and PMDD. Although CHC containing drospirenone is the only contraceptive FDA-approved for treating PMDD [53], a Cochrane review of five randomized controlled trials including 1920 women showed desogestrel-containing CHC may also improve mood symptoms [54]. As with menstrual migraines, preventing hormone fluctuations by administering extended-cycle regimens provides better control than monthly cyclical regimens [55–57]. A randomized trial comparing a contraceptive vaginal ring to oral CHC containing 30 μg EE and 3 mg drospirenone showed that both methods improved moderate to severe PMS similarly after 1 year of treatment [58].

A Cochrane review of progestin-only methods for treatment of PMS and PMDD found studies of poor quality and the results were inconclusive [59]. The full prescribing information for the Mirena IUD delineates all adverse reactions reported by more than 5% of subjects, and their data describes depression or depressed mood in 6.4% of users [60]. This is strikingly similar to the rate of pre-existing mood disturbances, as the annual prevalence of depression in the USA is 6.7% [61]. The Royal College of Obstetricians and Gynaecologists recommends against using LNG IUD as therapy for PMS, citing concerns about exacerbation of mood disorders [62].

Menstrual Suppression in Women with Disabilities

Gynecologic care for women with disabilities involves unique challenges, including susceptibility to sexual abuse, delayed screening for and diagnosis of sexually transmitted infections (STIs), and maintenance of menstrual hygiene [63]. ACOG has recommended the use of hormonal contraceptives for menstrual suppression in adolescents with disabilities [64]. This recommendation is echoed by the Canadian Task Force on Preventative Health Care [65••]. The most commonly used methods for menstrual suppression are extended or continuous CHC, DMPA, and LNG IUD [66]. However, CHC sometimes confers unacceptable risk of VTE in patients who have limited baseline motility or have medical comorbidities. DMPA may also confer a risk of decreased bone mineral density (BMD) with long-term use, which has led to a less frequent usage of DMPA for menstrual suppression in this population [66]. However, risks and benefits must be considered, and DMPA may continue to be the best therapy for menstrual suppression among many women. LNG IUD has been used safely and effectively for menstrual suppression with rates of amenorrhea comparable to DMPA—in one study, the amenorrhea rates of 44% at 6 months, 50% at 12 months, and 50% at 24 months were observed with LNG IUD [67].

Prevention and Treatment of Cancer

The protective effects oral CHC on ovarian cancer are well documented [68]. The mechanism is suspected to be due in part to fewer lifetime ovulations, as breastfeeding and parity are also known to be protective. This association holds true for women at increased risk of ovarian cancer. A case-control study including more than 1300 cases of ovarian cancer revealed that the protective effect of oral CHC appears to be dose-dependent, with the greatest protection against ovarian cancer noted with five or more years of use among BRCA1 mutation carriers (OR 0.50; 95% CI 0.40–0.63) and three or more years for BRCA2 mutation carriers (OR 0.42; 95% CI 0.22–0.83) [69••]. We expect that these findings can be extrapolated to non-oral CHC. Despite inconsistent prevention of ovulation, a population-based study from Finland showed that LNG IUD use was associated with decreased invasive and borderline ovarian tumors, but not primary fallopian carcinomas [70].

Data on the protective effects of contraception on the endometrium continue to emerge. Multiple large case-control studies have demonstrated that CHC use provides long-term protection against the development of endometrial cancer [71••, 72, 73]. A nationwide Finnish cohort study, including follow-up of more than 800,000 woman-years, examined the relationship between LNG IUD use and cancer diagnosis [74••]. Use of a single LNG IUD was associated with a 50% reduction in endometrial cancer (95% CI 0.35–0.70). Significant reductions in ovarian cancer (OR 0.60, 95% CI 0.45–0.76), pancreatic cancer (OR 0.5, 95% CI 0.28–0.81), and lung cancer (OR 0.68, 95% CI 0.49–0.91) were also noted. However, there was a small positive association with breast cancer (OR 1.19, 95% CI 1.13–1.25) and cancer overall (OR 1.07, 95% CI 1.03–1.11). The copper IUD is also

associated with lower rates of endometrial hyperplasia and cancer [75]. The mechanism underlying this finding is unclear, but it is hypothesized that alterations of the endometrial response to ovarian steroids and chronic inflammation lead to decreased endometrial mitotic activity and estrogen receptor concentrations [75]. Factors associated with the greatest endometrial protection with IUD use were duration greater than 10 years, use within the last year, and older age at initiation or discontinuation (>35 or >45 years, respectively) [76]. LNG IUD can also be used in the treatment of endometrial hyperplasia and cancer for women desiring fertility preservation as well as prevention of endometrial polyps among women on tamoxifen [75].

Multiple studies have demonstrated an inverse association between hormonal contraception and gastrointestinal cancers [73]. The most recent study supporting this relationship, a case-control study from Spain, showed an inverse relationship between age at first birth and gastric cancer risk (OR 0.69, 95% CI 0.53–0.9) as well as ever-use of hormonal contraception and decreased gastric cancer (OR 0.42, 95% CI 0.26–0.69), colon cancer (OR 0.64, 95% CI 0.48–0.86), and rectal cancer (OR 0.61, 95% CI 0.43–0.88) [77]. The mechanism underlying these associations is thought to be related to estrogen, but has not been fully elucidated.

Use of hormonal contraception is associated with a small increase in cervical and breast cancer risk. Many of the studies on CHC and breast cancer risk included women using older CHCs, and multiple studies including modern CHC formulations have failed to confirm the link [78, 79]. A systematic review and meta-analysis found that prior use of CHC was associated with breast cancer (OR 1.08, 1–1.17) and cervical cancer, although the odds ratios were small [73]. The meta-analysis on cervical cancer risk was not performed due to heterogeneity of the studies. The mechanism underlying the relationship between contraception and cervical cancer remains unclear and may be related to confounders such as sexual activity. IUD use is not associated with HPV acquisition, persistence, or clearance and observational data suggests that IUD use is inversely associated with cervical cancer, even after adjusting for a Pap smear frequency [80, 81]. A meta-analysis from the Royal College of Obstetricians and Gynecologists suggests that the net effect of hormonal contraception is a modest reduction in total cancer, with a hazard ratio of 0.88 (95% CI 0.83–0.94) [82].

Women undergoing treatment for cancer may require hormonal contraception for either pregnancy prevention or management of other medical conditions. Transdermal routes may cause skin or vaginal mucosa irritation in women receiving chemotherapy or radiation and progestin-only methods are more likely to cause initial abnormal uterine bleeding (AUB) and breakthrough bleeding but carry lower risk of venous thromboembolism (VTE) [83]. Adolescents with AUB as a result of cancer treatment may benefit from treatment with CHC or progestin-only methods [83].

Benign Breast Disease

Fibroadenoma is one of the most common benign breast tumors in young women and may be asymptomatic or associated with breast pain. A palpable breast mass can lead to an extensive work-up, accounting for up to 44–94% of breast lesion biopsies and over 500,000 surgical excisions per year [84, 85]. Use of CHC prior to the first full-term pregnancy has been associated with decreased risk of fibroadenoma [86]. In 2007, the Oxford Family Planning Association study updated its evaluation of over 17,000 women recruited from 1968 to 1974 and followed until 1994 [87]. The hospital referral rates for fibroadenoma and chronic cystic disease significantly declined with increasing duration of CHC use, but not with progestin-only pills.

Perimenopausal Use

Benefits of contraceptive hormone use in the perimenopausal years include reductions in menstrual migraines, abnormal bleeding, and hot flashes. In a study of 56 women over the age of 40, prolonged oral CHC formulations (24/4 and 84/7) reduced the frequency of menstrual migraines and withdrawal-related vasomotor symptoms [88]. Relatively few studies have been dedicated to evaluating the menstrual benefits of hormonal contraception among women over age 40, but given that menstrual irregularities in perimenopausal women are often a result of anovulatory cycles, it is reasonable to conclude that the benefits seen in younger women apply to older women too. In the absence of contraindications, age alone does not limit the use of hormonal contraception but an assessment of contraindications should always be performed. Abnormal uterine bleeding in perimenopausal patients should be evaluated prior to treatment initiation due to an increased risk of endometrial cancer in this population [89].

The progestin component of contraceptives can also provide endometrial protection during menopausal estrogen therapy (ET). Historically, oral progestins have been used monthly or every 3 months to prevent endometrial hyperplasia. A pooled analysis from six trials, including a total of 397 women, demonstrated that LNG IUD successfully prevents endometrial hyperplasia in perimenopausal and postmenopausal women using ET, with no cases of hyperplasia or carcinoma detected [90••]. Multiple estrogen formulations and doses were included in the studies, suggesting that LNG IUD is highly effective for endometrial protection in a variety of clinical situations. Continuous progestin exposure appears to provide superior protection compared to cyclical use of progestin, but is associated with more abnormal uterine bleeding [91].

Vaginal Microbiome

Vaginal flora plays an important role in gynecologic health. Alterations in the vaginal microbiome may lead to bacterial vaginosis (BV) which may increase transmission of STIs such as the human immunodeficiency virus (HIV) [92]. Beneficial increases in *Lactobacillus* species in women using estrogen-containing contraception are likely mediated through estrogen-induced glycogen accumulation in the vaginal epithelium, which supports the growth of lactobacilli [93]. A study of vaginal samples collected from 682 women as part of the Human Vaginal Microbiome Project found that women using oral CHC were more likely to have healthy lactobacilli microbiome compared with women relying on condoms for contraception [94]. Despite reports that the contraceptive vaginal ring is associated with increased vaginal discharge, a study of a novel 1-year CHC vaginal ring showed no increased risk of BV, candidiasis, or trichomoniasis when used in a cyclical manner [95], adding to the existing literature that shows the contraceptive ring does not increase the diagnosis of vaginitis or vaginosis [96].

Multiple studies show that both CHC and progestin-only methods such as DMPA protect against BV [97–99]. The effect of an IUD on the acquisition of BV is less clear. Some studies suggest an increased risk [100, 101] while others show no association [102], particularly with hormonal IUDs [99, 103]. A prospective study published as part of the Contraceptive CHOICE Project showed no association between IUD use and BV, after controlling for confounders, although results were not stratified by IUD type [104••]. In this study, irregular vaginal bleeding predicted the development of BV, which may underscore the relationship between menstrual bleeding and BV [105].

Conclusion

In summary, contraception has numerous benefits beyond pregnancy prevention. While therapeutic use of contraception remains "off-label" for some of these conditions, there is ample evidence to recommend contraception for the treatment and prevention of menorrhagia, dysmenorrhea, abnormal uterine bleeding, pelvic pain, PCOS and hyperandrogenism, PMS, PMDD, menstrual migraines without aura, and endometrial hyperplasia. Further, patients using contraception for pregnancy prevention can be counseled on beneficial effects related to breast fibroadenoma, ovarian cancer risk, and endometrial cancer risk. Evidence continues to emerge on the effects of contraception on genital tract flora and non-gynecologic cancers.

Compliance with Ethical Standards

Conflict of Interest Ashley R. Brant and Stephanie J. Teng declare that they have no conflicts of interest.

Peggy Peng Ye declares owning approx. 200 shares of stock in Merck, the pharmaceutical company that manufactures the contraceptive implant.

Pamela S. Lotke declares personal fees for advisory board work for Bayer Healthcare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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