Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods

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BACKGROUND: Most contraceptive methods present benefits beyond contraception; however, despite a large body of evidence, many healthcare professionals (HCPs), users and potential users are unaware of those benefits. This review evaluates the evidence for non-contraceptive benefits of hormonal and non-hormonal contraceptive methods.

METHODS: We searched the medical publications in PubMed, POPLINE, CENTRAL, EMBASE and LILACS for relevant articles, on non-contraceptive benefits of the use of hormonal and intrauterine reversible contraceptive methods, which were published in English between 1980 and July 2014. Articles were identified using the following search terms: ‘contraceptive methods’, ‘benefits’, ‘cancer’, ‘anaemia’, ‘heavy menstrual bleeding (HMB)’, ‘endometrial hyperplasia’, ‘endometriosis’ and ‘leiomyoma’.

RESULTS: We identified, through the literature search, evidence that some combined oral contraceptives have benefits in controlling HMB and anaemia, reducing the rate of endometrial, ovarian and colorectal cancer and ectopic pregnancy as well as alleviating symptoms of premenstrual dysphoric disorder. Furthermore, the use of the levonorgestrel-releasing intrauterine system also controls HMB and anaemia and endometrial hyperplasia and cancer, reduces rates of endometrial polyps in users of tamoxifen and alleviates pain associated with endometriosis and adenomyosis. Depot medroxyprogesterone acetate controls crises of pain associated with sickle cell disease and endometriosis. Users of the etonogestrel-releasing contraceptive implant have the benefits of a reduction of pain associated with endometriosis, and users of the copper intrauterine device have reduced rates of endometrial and cervical cancer.

CONCLUSIONS: Despite the high contraceptive effectiveness of many hormonal and intrauterine reversible contraceptive methods, many HCPs, users and potential users are concerned mainly about side effects and safety of both hormonal and non-hormonal contraceptive methods, and there is scarce information about the many benefits that these methods offer beyond contraception.

Key words: non-contraceptive benefits / levonorgestrel-releasing intrauterine system / oral contraceptives / depot medroxyprogesterone acetate / copper intrauterine device
Introduction

Hormonal and non-hormonal contraceptives were initially developed to prevent unplanned and unintended pregnancy. However, since the first combined oral contraceptive (COC) was introduced in the USA and European markets (Chang, 1978; Szarewski et al., 2010), many studies have demonstrated that the use of this kind of contraception may have considerable non-contraceptive benefits. The most important research areas have been the link between COC use and the reduced risk for gynaecological cancers, and their use in treatment of irregular and heavy menstrual bleeding (HMB) and dysmenorrhoea (Shulman, 2011). Nevertheless, with the widespread use of hormonal and non-hormonal methods, many healthcare providers (HCPs) are concerned about the side effects and risks associated with the use of hormonal contraceptives (Bitzer et al., 2013); therefore, little has been presented about non-contraceptive benefits. Additionally, the lay press has influenced many women’s ideas concerning the risks and side effects of contraceptives. Women who are well-informed about the effectiveness of contraceptives, their side effects and their non-contraceptive benefits are more likely to use them and consequently avoid unplanned pregnancies.

The objective of this review is to assess the evidence regarding the non-contraceptive benefits of hormonal and non-hormonal contraceptives in order to strengthen knowledge of HCPs in an area that is somewhat neglected.

Methods

We searched medical publications in PubMed, POPLINE, CENTRAL, EMBASE and LILACS for relevant articles, on non-contraceptive benefits from the use of contraceptive methods, which were published in English between 1980 and July 2014. Articles were identified using the following terms: ‘contraceptive methods’, ‘hormonal contraceptives’, ‘intrauterine contraceptives’, ‘copper IUD’, ‘benefits’, ‘cancer’, ‘anaemia’, ‘heavy menstrual bleeding’, ‘endometrial hyperplasia’, ‘endometriosis’, and ‘leiomyoma’. We reviewed and included relevant publications as appropriate. Case reports were not included.

Results

Combination hormonal contraceptives

COCs combine an estrogen and a progestin in a single tablet that is ingested orally once daily in a variety of dosing regimens ranging from conventional 21 active and 7 hormone-free tablets to reduced hormone-free interval regimens (e.g. 24/4) to regimens with some days of low-dose estrogen-only tablets in lieu of placebo tablets to continuous-use regimens. Most COCs employ ethinyl estradiol (EE) for the estrogen component, although estradiol-based pill regimens have been recently introduced. In contradistinction to the few estrogenic compounds available in COCs, there is a wide array of contraceptive progestins available in COCs, with most of the older progestins being derived from testosterone, new compounds not derived from testosterone like nomegestrol acetate and dienogest (DNG) and other novel progestins such as drospirenone (DRSP) being derived from spirolactone.

COCs exert their contraceptive effect by two different mechanisms: ovulation inhibition and the progestin component that prevents the luteinizing hormone surge required for release of the ovum. The estrogen component of the pill also serves to provide a more tolerable and acceptable bleeding profile by proliferating and stabilizing the endometrium during the days of exogenous estrogen ingestion with subsequent sloughing of the endometrium (i.e. withdrawal bleed) upon discontinuation of hormonal ingestion during the pill-free days. Estrogens also serve to augment contraceptive efficacy by inhibiting the release of follicle-stimulating hormone from the pituitary, thus further inhibiting the development of the dominant follicle and preventing release of the ovum (Shulman, 2013).

The non-contraceptive benefits associated with COC use derive primarily from its mechanisms of action: ovulation inhibition and local progestin effects on the endometrium and genital tissue. While the precise aetiology of the non-contraceptive benefits have not been completely delineated, the epidemiological impact of COC use on the following clinical outcomes has been well described and is an important aspect of oral contraceptive use worldwide. Indeed, despite anecdotal reports and reports in the lay press to the contrary, COCs provide a considerably positive benefit-to-risk ratio for users, with much of this positive impact resulting from the non-contraceptive benefits associated with conventional COC use (Burkman et al., 2001). A summary of the benefits associated with the use of combination hormonal contraceptives is presented in Table I.

Heavy menstrual bleeding

HMB is a common but challenging health condition. HMB is commonly defined in research protocols as menstrual flow exceeding 80 ml of blood loss per menstrual cycle that cannot be explained by organic pathology or medical illness. However, the clinical diagnosis is invariably subjective and does not typically involve the measurement of actual menstrual blood loss. In addition, laboratory values that assess anaemia are not necessarily of value in arriving at a correct diagnosis, as many women with HMB may not show any laboratory evidence of anaemia. As such, clinicians must rely on the reported perceptions by women as to what is an ‘acceptable’ blood loss, recognizing that these perceptions may not provide an accurate assessment of a woman’s actual blood loss and whether further evaluation and intervention is needed.

Early anecdotal evidence strongly supported the impact of COCs on reducing menstrual bleeding volumes along with reducing unscheduled bleeding. However, a Cochrane Collaboration review (Farquhar and Brown, 2009) of COCs for HMB found only one randomized trial that met its inclusion criteria; the paucity of robust data thus meant that the review authors could not meet their inclusion criteria. The eligible trial, a crossover study of mefenamic acid, low-dose danazol, naproxen and a COC (30 μg EE and 150 μg levonorgestrel [LNG] in a 21/7 regimen), found reductions in HMB approaching 50%, but no significant differences among the various agents tested (Fraser and McCarron, 1991). A more recent review (Hoaglin et al., 2013) of several ‘treatment classes’ (COCs, danazol, endometrial ablation, LNG-releasing intrauterine system [LNG-IUS], placebo, progestins given for <2 weeks out of 4 during the menstrual cycle [short-term], progestins given for close to 3 weeks out of 4 [long-term], and tranexamic acid) found that the LNG-IUS and endometrial ablation provided the greatest reduction in blood loss among women with HMB, but that COCs were effective and comparable with long-term progestin therapy and danazol and superior to short-term progestin therapy, tranexamic acid and placebo.

Two recent studies of newer estradiol (E2)-based COC regimens provide robust evidence that such regimens are effective in reducing
Table 1 Summary of benefits associated with the use of combined oral contraceptives (COCs).

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Heavy menstrual bleeding (HMB)</td>
<td>Not all COCs provide a reduction in blood loss among women with HMB; however, it is likely that women will experience a considerable reduction in cyclic blood loss (Fraser et al., 2011; Jensen et al., 2011).</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Women who used continuously a COC presented a reduction in the recurrence of dysmenorrhea, reduction in pelvic pain and lower recurrence of endometrioma (Zorbas et al., 2015).</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Data from the past consistently 35 years support the risk-reducing effect of routine COC use on the risk of developing endometrial cancer (Dossus et al., 2010; Hanaaford et al., 2010 [RR 0.43; 95% CI 0.21–0.88]).</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Worldwide use of COC prevents an estimated 30,000 deaths from ovarian cancer annually; a significant risk reduction has been shown (OR 0.73; 95% CI 0.66–0.81).</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>The literature is consistent in showing a reduced risk for colorectal cancer among COC users (Bosetti et al., 2009 [RR 0.81; 95% CI 0.72–0.92]).</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>The ability of COC use to reduce the risk of pelvic inflammatory disease may provide a mechanism by which COC use reduces the risk of ectopic pregnancy (Burkman et al., 2004).</td>
</tr>
<tr>
<td>PMDD</td>
<td>COC with 20 μg EE combined with 3 mg drospirenone in a 24/4 regimen, when compared with placebo, significantly reduced the physical and emotional symptoms of PMDD (Pearlstein et al., 2005; Yonkers et al., 2005; Coffee et al., 2006).</td>
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PMDD: pre-menstrual dysphoric disorder; RR: relative risk; OR: odds ratio; CI: confidence interval.

HMB. Ahrendt et al. (2009) compared a COC regimen containing E2 valerate (E2V) and DNG with a regimen containing EE and LNG and found that women using the newer E2-based regimen with E2V/DNG reported shorter and lighter withdrawal bleeds that those reported by women using the older and more conventional EE regimen. In addition, women using the E2V/DNG regimen reported significantly fewer overall bleeding and spotting days during the first 90 days of use than those using the EE-based regimen. More recently, Fraser et al. (2011) and Jensen et al. (2011) both showed, in randomized, double-blinded, placebo controlled trials (RCTs), that the E2V/DNG COC significantly reduced HMB compared with placebo. It is clear that while COCs may not provide the greatest reduction in blood loss among women with HMB, women who use COCs can expect a reduction in menstrual/withdrawal bleeding volume and those with HMB will likely experience a considerable reduction in cyclic blood loss. Unfortunately, there are no published ‘head-to-head’ trials comparing specific COC regimens with regard to their impact on reduced blood loss. However, anecdotal evidence and more recent and robust clinical trials all suggest that COCs, especially newer and lower-dosed COCs, all reduce the volume of blood loss with conventional use.

Endometriosis after surgical treatment

Surgical and medical treatments for endometriosis have the purpose of relieving pain, reducing the stage of the disease and/or enhancing fertility, as well as destroying/removing endometriotic foci including ovarian endometriomas when appropriate. Many researchers have proposed the use of an adjunctive post-operative medical therapy and this has been used mainly to reduce the pain-associated endometriosis. COCs could be one of the best choices because it is safe in the long-term and well tolerated. In a recent systematic review (Zorbas et al., 2015), the authors evaluated studies that met the following criteria: (i) post-operative treatment with both continuous and cyclic COC, (ii) minimum 6 months duration of treatment and (iii) at least 12 months of follow-up. The authors observed that women who continuously used a COC presented a reduction in the recurrence of dysmenorrhea, a reduction in pelvic pain and a lower recurrence of endometrioma.

Endometrial cancer

A reduction in the risk for endometrial cancer among users of COCs has long been reported in the literature. Weiss and Sayvetz (1980) reported a 50% reduction in endometrial cancer rates among users of COCs that were, at the time, administered at considerably higher-dosed than regimens used today. The mechanism of endometrial cancer risk reduction is believed to be the overall suppressive effect of COCs on endometrial proliferation along with effective sloughing of the endometrial lining with timed hormone-free intervals; the risk-reducing effect of COCs on the development of endometrial cancer persists after discontinuation.

More recent studies continue to affirm the endometrial cancer risk-reducing characteristics of COCs. Hanaaford et al. (2010) reported outcomes from the Royal College of General Practitioners (UK) database that showed that when compared with never-users of COC, ever-users were characterized by a significant reduction in the risk of endometrial cancer [relative risk (RR) 0.43; 95% CI 0.21–0.88]. This same study also showed significantly lower mortality rates from all cancers (including large bowel/rectum and ovarian cancer), as well as reduced mortality from ischaemic heart disease. Dossus et al. (2010) reported outcomes from the European Prospective Investigation into Cancer and Nutrition study and again found that users of COCs were at a significantly reduced risk of developing endometrial cancer (HR 0.65; 95% CI 0.56–0.75).

The consistency of these data spanning the past 35 years supports the risk-reducing effect of routine COC use on the risk of developing endometrial cancer. Despite the fact that many physicians recognize the role of COCs in reducing the risk for endometrial cancer, COCs are uncommonly prescribed for prevention of endometrial cancer (Horst and Modesitt, 2014).

Ovarian cancer

Similar to the effect observed among COC users on the risk of endometrial cancer, a comparable reduction in risk of epithelial ovarian cancer (EOC) has been observed among users of COCs. The degree of risk reduction is associated with length of COC use; that is, the longer the duration of use of COCs, the greater the risk reduction (Risch et al., 1983). Beral et al. (2008) on behalf of the Collaborative Group on Epidemiologic Studies of Ovarian Cancer reported that the worldwide use of COC
prevent an estimated 30,000 deaths from ovarian cancer annually. A recent meta-analysis showed a significant and clinically relevant reduction in ovarian cancer incidence in ever-users compared with never-users [odds ratio (OR) 0.73, 95% CI 0.66–0.81], characterized by a significant duration—response relationship, with a reduction in incidence of >50% among women using COCs for 10 or more years (Havrilesky et al., 2013).

What is not similar to the risk-reducing effect of COCs on endometrial cancer is the lack of a distinct biological mechanism explaining the risk-reducing effect of COCs on the development of EOC. It has long been postulated that reduction/elimination of ovulation would reduce the risk of EOC, as has been observed with ovulation inhibiting conditions such as pregnancy, breastfeeding and the use of COCs. In this direction, another hormonal contraceptive, which also inhibits ovulation, depot medroxyprogesterone acetate (DMPA), has been shown to reduce the risk of EOC. A recent study (Wilailak et al., 2012) showed that the use of DMPA was associated with a 39% reduction in the risk of EOC (OR 0.61; 95% CI 0.44–0.85; P = 0.002). Furthermore, 83% of the risk reduction was observed among users for >3 years (OR 0.17; 95% CI 0.07–0.39; P < 0.001).

The risk-reducing effect of COCs may also be the result of a direct effect of contraceptive hormones, and in particular progestins, on the ovarian epithelial surface. This may explain the lack of consistent findings in EOC risk reduction among ovulation suppression therapies (Rodriguez et al., 2013). In a study of macaque monkeys treated either with combination OCs or with their individual estrogen or progestin components or with controls, a significant increase in apoptosis of the ovarian epithelium was demonstrated in the groups receiving progestins, either alone or in combination with an estrogen (Rodriguez et al., 1998). An increase in apoptosis would potentially eliminate cells that have sustained genetic damage and may be predisposed to develop into a malignancy (Canman et al., 1994). Indeed, Schildkraut et al. (2002) reported an increase in the risk-reducing impact of COCs on the risk of EOC when contraceptive regimens incorporating a high potency progestin were used. That progestins apparently activate this critical pathway in the ovarian epithelium raises the possibility that progestin-mediated apoptotic effects, and not solely inhibition of ovulation, may be responsible, and provide a second plausible biological mechanism, for the reduction in ovarian cancer risk that is associated with COC use. At this time, it is best to consider that the mechanisms resulting in a reduced risk for EOC among COC users are likely a combination of the aforementioned mechanisms or other as yet unrecognized biological processes.

Although there are several potential mechanisms for the risk-reducing effect of COCs on EOC, recent pathogenic data now suggest that many high-grade serous EOCs arise not from the ovarian epithelium but from the distal fallopian tube (Reade et al., 2014). Consistent with the epidemiological data regarding COC use, early work demonstrates that the fallopian tube epithelium is influenced by ovulatory cycles, with ovulation exerting an inhibitory effect (Donnez et al., 1985). Accordingly, all the potential mechanisms attributable to a salutary effect on the ovary may also be relevant to a similar effect on the fallopian tube.

Regardless of the mechanism(s) of action, the use of COCs has become a staple of the management of reproductive-aged women at increased risk for developing EOC (Shulman and Dungan, 2010), especially those with BRCA1/2 mutations who wish to maintain their reproductive capabilities (Gadducci et al., 2013). However, there is some controversy as to whether COC use in BRCA1/2 mutation carriers increases their risk of developing breast cancer. More recent assessments continue to show disparate outcomes, although the studies that do demonstrate an increased risk for breast cancer among BRCA1/2 mutation carriers who use COC consistently show that the increased risk is small and in those studies that show statistical significance, and that epidemiological benchmark is barely met. This calls into question the clinical relevance of such findings. Iodice et al. (2010) showed no increased risk of breast cancer among COC users, whereas Moorman et al. (2013) showed an increased risk (OR 1.21) that did not reach statistical significance (95% CI 0.93–1.58). Havrilesky et al. (2013) showed a small increased risk of breast cancer (OR 1.08) among COC users at an increased risk of developing ovarian cancer, but this increased risk barely achieved statistical significance (95% CI 1.00–1.17). While some of the disparate findings are clearly attributable to the performance of meta-analyses, an overview of these most recent studies indicates that the benefits of risk reduction for EOC in high-risk women through the routine use of COCs are not minimized by a clinically relevant increased risk of breast cancer in such users.

**Colorectal cancer**

Although fewer studies among COC users have examined colorectal cancer (CRC) compared with endometrial and ovarian epithelial cancers, the literature is likewise consistent in showing a reduced risk of CRC among COC users. Bosetti et al. (2009) showed an approximate 20% reduction in both colon and rectal cancers (RR 0.81; 95% CI 0.72–0.92). As opposed to the increased duration of COC use resulting in an increased reduction in risk for endometrial cancer and EOC, this study appears to suggest that the protection against CRC is stronger among current users (Bosetti et al., 2009).

Another difference is that the association between COC use and CRC risk reduction lacks a defining mechanism(s) of action. Newcomb et al. (2008) have reviewed several potential mechanisms that range from a direct effect of hormones on colorectal mucosa to genetic and epigenetic phenomena. Nonetheless, the epidemiological findings provide confidence in the use of COCs for CRC risk reduction, especially among reproductive-aged women with Lynch syndrome who can potentially find considerable benefit from COC use to reduce their increased risk for endometrial, colonic and ovarian epithelial malignancies (Lu and Daniels, 2013).

**Ectopic pregnancy**

The primary mechanism by which COCs reduce the risk of ectopic pregnancy is by providing effective pregnancy prevention. However, the ability of COC use to reduce the risk of pelvic inflammatory disease may provide a second but important mechanism by which COC use considerably reduces the risk of ectopic pregnancy (Burkman et al., 2004). What is not clear is whether the risk of ectopic pregnancy is increased among those few women who conceive while on COCs. There is evidence that women who become pregnant while on progestin-only oral contraceptives may have a higher likelihood of that pregnancy being extrauterine (Furlong, 2002).

**Symptoms of premenstrual dysphoric disorder**

The relief of symptoms of premenstrual dysphoric disorder (PMDD) is a benefit apparently associated with only specific COC regimens. Early studies evaluating a variety of monophasic and multiphasic regimens...
failed to demonstrate a benefit of COCs in improving premenstrual mood, despite the ability of COCs to inhibit ovulation and thus prevent the hormonal changes that were believed to be associated with menstrual-related mood disorders. Joffe et al. (2003) concluded that ‘oral contraceptive pills do not influence premenstrual mood in most women’.

However, two subsequent studies (Pearlstein et al., 2005; Yonkers et al., 2005) evaluating a 20-µg EE formulation combined with 3-mg DRSP in a 24/4 regimen found that, when compared with placebo, the physical and emotional symptoms of PMDD were significantly reduced. Around the same time, a study comparing a 30-µg EE/3-mg DRSP tablet in a conventional 21/7 regimen with an extended use (168 days) regimen incorporating the same tablet found a significant improvement in premenstrual symptoms among users of the extended regimen (Coffee et al., 2006). While neither of these DRSP regimens were evaluated in the treatment of PMDD, both regimens were effective in reducing premenstrual physical and mood symptoms.

**Progestin-only contraception: the LNG-IUS**

The LNG-IUS (Mirena, Bayer Oy, Turku, Finland) was developed by Prof. Tapani Luukkainen, the Population Council’s International Committee for Contraception Research and the former Finnish company Leiras Oy (Nilsson et al., 1981; Luukkainen et al., 2001).

**Heavy menstrual bleeding**

This highly effective contraceptive method has several non-contraceptive benefits, the most important one being the treatment of women with HMB. This effect was observed as early as the initial clinical trials: the users showed lighter uterine bleeding, with a variable proportion of women showing no bleeding during use (amenorrhoea). Furthermore, up to 60% saw an improvement in haemoglobin, iron stores and reduction of anaemia (Kaunitz et al., 2010, 2012). In 1990, researchers objectively measured a reduction in menstrual bleeding in women with HMB (pretreatment blood losses between 80 and 400 ml; Andersson and Rybo, 1990) and they showed 90, 95 and 98% reductions in menstrual blood loss for up to 3, 6 and 12 months, respectively, after insertion, and at 1 year, no woman had an objective blood loss of >20 ml. After this initial study, many subsequent studies have been published confirming these initial findings (Marjoribanks et al., 2006; Kaunitz et al., 2009).

Other authors observed 79, 84, 98 and 85% reductions in blood loss at 6, 12, 24 and 36 months, respectively, after LNG-IUS insertion (Xiao et al., 2003). In fact, the use of the LNG-IUS for the treatment of HMB is approved in almost 100 countries and has been compared with endometrial ablation (Kaunitz et al., 2009) and oral medroxyprogesterone acetate (MPA; Kaunitz et al., 2010); its efficacy is almost equal or superior, with an overall risk of failure of 13.4% (Kaunitz et al., 2009). Furthermore, the use of the LNG-IUS in women with HMB was compared in several studies with hysterectomies. It was found that both treatments were equally effective in the majority of the treated women at up to 10 years of follow-up (Hurskainen et al. 2004; Reid and Mukri, 2005; Helio¨vaara-Peippo et al., 2013), albeit that 50% of the women had a hysterectomy during the 10 years of observation and amenorrhoea was more common among the women who underwent surgery. However, the LNG-IUS was more cost-effective than hysterectomy (Middleton et al., 2010; Bahamondes et al., 2012).

The LNG-IUS is effective for the treatment of HMB due to different causes, including women with non-structural pelvic abnormalities such as disorders of haemostasis like von Willebrand’s disease, platelet disorders, coagulation deficiencies and anticoagulant drugs (Kingman et al., 2004; Schaedel et al., 2005; Kadir and Chi, 2007; Lukes et al., 2008; Vilos et al., 2009; Hale et al., 2010). Many HCPs consider the LNG-IUS a first choice for women with HMB and disorders of haemostasis. Regarding HMB associated with structural pelvic abnormalities, the most common is uterine fibroids, and the insertion of an LNG-IUS is effective in the treatment of HMB for these women, although less effective when compared with women with HMB without fibroids, and there is no effect on the reduction of the size of the fibroids (Grigorieva et al., 2003; Mercorio et al., 2003; Soysal and Soysal, 2005; Kaunitz, 2007).

In a recent UK-based RCT (Gupta et al., 2013), the authors compared the use of the LNG-IUS and the usual medical treatment (tranexamic acid, mefenamic acid, combined estrogen–progestogen or progestrone alone) in 571 women with HMB over a 2-year period through the menorrhagia multi-attribute scale. They observed an improvement in both treatment groups and found that the improvements were significantly greater in the LNG-IUS group and were maintained through the 2-year period of the evaluation (P < 0.001). Furthermore, 64% of the women were still using the LNG-IUS whereas 38% were still using the usual medical treatment (P < 0.001).

Several publications have shown that the reduction of blood loss in women with HMB after insertion of an LNG-IUS is followed by an improvement of body iron stores as evidenced by an increase in haemoglobin and serum ferritin (Imperato et al., 2002; Xiao et al., 2003). Additionally, the authors evaluated the impact of anaemia and iron deficiency provoked by HMB on health-related quality of life (QoL). Women whose anaemia improved also reported an improved QoL (Peuranpää et al., 2014; Xu et al., 2014).

**Endometrial hyperplasia**

The use of LNG-IUS in the treatment of endometrial hyperplasia is off-label in many countries; however, there are some cases in which it was used mainly among young women who wanted to preserve their fertility. A meta-analysis (Gallos et al., 2010) of studies that evaluated the treatment of simple endometrial hyperplasia with LNG-IUS or oral progestogens found that LNG-IUS showed higher regression rates than oral progestogens for simple hyperplasia (pooled rate = 92 versus 66%; P < 0.01) and atypical hyperplasia (pooled rate = 90 versus 69%; P = 0.03).

In a comparative study (Gallos et al., 2013a), the authors evaluated 344 patients with complex non-atypical or simple endometrial hyperplasia, whom they treated with an LNG-IUS (n = 250) or oral progestins (n = 94). Regression of hyperplasia was observed in 94.8% (237/250) or 84.0% (79/94) of the patients with an LNG-IUS or progestin, respectively (adjusted OR = 3.04, 95% CI 1.36–6.79; P = 0.001). Furthermore, the proportion of women who underwent a hysterectomy was lower (22.1%, 55/250 versus 37.2%, 35/94; adjusted OR = 0.48, 95% CI 0.28–0.81; P < 0.004) with the use of the LNG-IUS when compared with the oral progestin.

These findings are similar to previous studies with lower numbers of cases. One prospective study (Varma et al., 2008) used an LNG-IUS to treat 105 women with endometrial hyperplasia. The results showed that endometrial regression was achieved in 90% of the cases by 2 years, and most of the cases (96%) achieved regression within 1 year. Regression occurred in 92% and 67% of the cases with simple
and atypical hyperplasia, respectively. Other authors (Gallos et al., 2013b) observed similar results; furthermore, they found that the main variable associated with failure of treatment with an LNG-IUS was body mass index (BMI) \( \geq 20 \) (HR = 5.51, 95% CI 1.05–28.87; \( P = 0.043 \)). Relapse was observed in 12.7% of cases within 9 years of follow-up (median = 67 months), and again, a BMI \( \geq 35 \) was the independent predictor of relapse (HR = 18.93, 95% CI 3.93–91.15; \( P < 0.001 \)).

**Endometrial and ovarian cancer**

The LNG-IUS was recently associated with a protective effect against endometrial and ovarian cancer. A recent Finish-based study (Soini et al., 2014) evaluated the association between use of the LNG-IUS among premenopausal women and the incidence of endometrial cancer, mainly endometrial adenocarcinoma. The authors evaluated all Finnish women aged 30–49 years who used an LNG-IUS due to HMB \((n = 93,843)\). They identified 2781 cancer cases among LNG-IUS users during the follow-up of 855,324 women-years. The observed-to-expected ratio for endometrial adenocarcinoma was 0.50 (95% CI 0.35–0.70; 34 observed compared with 68 expected cases) after the first use of LNG-IUS period and 0.25 (95% CI 0.05–0.73; 3 observed compared with 12 expected cases) after the second use. Furthermore, the standardized incidence ratio for ovarian cancer was 0.60 (95% CI 0.45–0.76; 59 observed compared with 99 expected cases). The possible mechanism associated with the use of the LNG-IUS and the protective effect for endometrial cancer could be the down-regulation of estrogen receptors, which results in low endometrial cellular proliferation and, in many cases, amenorrhea (Luukkainen et al., 2001).

**Endometrial polyps in users of tamoxifen**

A systematic review (Chin et al., 2009) evaluated the use of the LNG-IUS among female users of tamoxifen in RCTs and showed that the LNG-IUS users presented a significant reduction in the incidence of endometrial polyps (Peto OR = 0.14, 95% CI 0.03–0.61; Gardner et al., 2000, 2009; Chan et al., 2007). Wong et al. (2013) conducted an RCT with 129 women with breast cancer and who were users of tamoxifen; the women were randomized to LNG-IUS before initiation of tamoxifen intake or no treatment. The uterine cavity was evaluated at 12, 24, 45 and 60 months after baseline. No cases of endometrial hyperplasia were recorded in either groups; however, LNG-IUS reduced endometrial polyps \( \text{de novo} \) (HR = 0.19, 95% CI 0.07–0.48). Additionally, Arnes et al. (2014) evaluated 59 women with hyperplastic polyps; the women received an LNG-IUS, 10 mg of oral MPA (10 days per cycle) or only observation for 6 months. The numbers of women without polyps after 6 months were 18 of 18 for those who received an LNG-IUS, 5 of 20 for women treated with cyclic MPA (25%) and 2 of 21 (9%) for those without any treatment.

**Pain associated with endometriosis**

The use of the LNG-IUS for the treatment of pain associated with endometriosis is off-label in many countries; however, there are many publications showing that this kind of treatment is effective in pain alleviation. The most important symptoms beyond infertility are dysmenorrhea and non-cyclical pelvic pain. The gold standard medical treatment is still the use of gonadotrophin-releasing hormone (GnRH) analogues; however, there is evidence showing that the insertion of an LNG-IUS is an adequate medical treatment for endometriosis and comparable with the use of GnRH with the advantage that it is possible to use it for up to 5 years and does not interfere with bone mineral density (Bahamondes et al., 2010).

We identified some RCTs in which the authors presented data about the use of the LNG-IUS after conservative surgery, a comparison between the LNG-IUS with surgical treatment, a comparison with DMPA and studies that compared it with GnRH-a (Vercellini et al., 2003; Petta et al., 2005; de Sá Rosa e Silva et al., 2006; Gomes et al., 2007; Bayoglu Tekin et al., 2011; Tamhahasamut et al., 2012). The results showed that both the LNG-IUS and GnRH-a reduced pain scores according to the visual analogue scale without significant differences between both groups, although amenorrhea occurred more rapidly among the GnRH users than the LNG-IUS users. Additionally, both treatments improved the staging scores in a similar manner and improved QoL. Others authors also showed an improvement in endometriosis staging after insertion of the LNG-IUS (Lockhat et al., 2005).

Despite the body of evidence regarding the improvement of pain associated with endometriosis and adenomyosis after the insertion of LNG-IUS, this kind of treatment is still considered to be a second line of therapy until more robust evidence can be obtained (Abou-Setta et al., 2006; Johnson et al., 2013). It is unclear what the mechanism of action of the LNG-IUS to relieve pain associated with endometriosis is; however, it probably involves high levels of LNG intrauterine and some systemic effects because after the insertion, a depletion of estrogen and progesterone receptors and a reduction of endometrial cell proliferation occur (de Sá Rosa e Silva et al., 2006).

**Pain associated with adenomyosis**

Adenomyosis is another disease that benefits from insertion of the LNG-IUS because patients needed to reduce menstrual blood loss and pain via a reduction in thickness of the myometrial junctional zone and total uterine volume. Nevertheless, it has been described that the efficacy of the LNG-IUS on the reduction of uterine volume only begins to decrease after 2 years of placement (Cho et al., 2008). There are improvements in two directions: HMB and pain associated with adenomyosis. The first improvement could be attributed to direct effect of the LNG on foci of adenomyosis with decidualization and hypotrophy or atrophy of the endometrium (Fong and Singh, 1999; Haberal et al., 2006). The improvement on pelvic pain has been well documented and plausible explanations could be the effects of LNG on the endometrium or on the vascular supply to the pelvis allowing relief from pelvic congestion. However, anecdotal reports indicate that the LNG-IUS should probably be replaced before its 5-year life span (Fedele et al., 1997; Fong and Singh, 1999; Braghetto et al., 2007; Cho et al., 2008). The aforementioned studies did not include control women.

**Progestin-only contraception: DMPA**

**Sickle cell disease**

Sickle cell disease (SCD) is an inherited haematological disease without the possibility of cure and caused by abnormal haemoglobin that distorts red blood cells into sickle shapes. This kind of cell can block small blood vessels, impairing the transport of oxygen to the body’s tissues and provoking episodes of bone pain known as sickle pain crises, chronic complications and a life expectancy of 48 years on average (Platt et al., 1994). Women with SCD present chronic haemolysis, which is associated with anaemia, reticulocytosis and high levels of fetal haemoglobin. As a consequence, it is possible that affected patients present venous stasis,
blood hyperviscosity, vaso-occlusion and tissue infarction. The sickle crisis is the result of vaso-occlusion, which can also provoke retinopathy, nephropathy, asplenia, stroke and eventually infection (Booth et al., 2010; Rees et al., 2010).

SCD has special relevance in Caribbean, Latin American, Arabic, Indian, Mediterranean countries and sub-Saharan Africa, where the prevalence is the highest (Munker et al., 2000). However, with migration, it is possible to find it in patients anywhere. As an example, the estimated number of subjects affected in the USA is 70 000–100 000 (Hassell, 2010), and among African Americans in the USA, it is almost 1 in 500 (National Heart, Lung, and Blood Advisory Council, 2011). Furthermore, pregnancy in affected women is associated with high maternal and fetal mortality and morbidity rates.

A UK survey showed that 64% of women with SCD had experienced an unintended pregnancy; however, in a newer survey (Eissa et al., 2015), this declined to 53%. There is no doubt that women with SCD need effective contraception, and it is desirable that the method also provides some benefits to the disease. Although the use of hormonal contraceptives for SCD is controversial in the scientific literature (Manchikanti et al., 2007; Haddad et al., 2012), most types of contraceptives can be used in women with SCD. Progesterone may stabilize the erythrocyte membrane and may prevent sickle crises (Issacs and Hayhoe, 1967; Issacs et al., 1972), while DMPA stabilizes the red cell membranes, making them less prone to sickling, thus causing reductions in pain crises (ACOG Practice Bulletin, 2006).

One crossover study randomized women to receive up to three DMPA injections (150 mg IM) or saline injections (1 ml IM) administered every 3 months. A total of 29 episodes of pain were recorded among the 23 patients under evaluation during weeks 0 to 30 of the DMPA phase. This is in contrast with 58 episodes among 20 of the 23 patients during the treatment with the placebo (OR = 0.23, 95% CI 0.05–1.02). There were six patients who did not present differences whether exposed to DMPA or placebo; however, the other 17 patients presented more painful crises during the placebo phase (13 patients) when compared with the DMPA phase (4 patients) (P ≈ 0.05). This study from De Ceulaer et al. (1982) resulted in a significant improvement; however, it has been reported that serum levels of DMPA were detected up to 200 days after the last injection (Kirton and Cornette, 1974), and consequently, the short crossover period could have biased the results. If during the washout period there were still DMPA levels present in the women’s systems, those who started the study with DMPA may have had some serum levels of the steroid at the beginning of the placebo period, potentially decreasing the painful crises during the placebo phase and thus underestimating the DMPA effect.

Another study compared the DMPA group, a COC group and a non-user group in 43 women with SCD (Abood et al., 1997). The authors reported that among users of DMPA, only 30% reported crises at the end of the first year of use in comparison with 46 and 50% among users of COC and non-users, respectively. However, the blood parameters did not show any change through the year of observation, which is contrary to the other two publications (Issacs et al., 1975), which observed improvements in haematocrit and prothrombin time.

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Pain associated with endometriosis
Endometriosis is a chronic disease, and one of the main problems affected women experience is chronic menstrual and non-menstrual pelvic pain including dysmenorrhea and dyspareunia. The disease is estrogen-dependent and it is reported that improvement in the disease and regression of the lesions occurs in women treated with drugs inducing ovarian suppression or amenorrhoea or in women after menopause. DMPA has been used in several trials to treat pain associated with endometriosis. One RCT comparing DMPA (150 mg IM injection every 3 months) showed similar pain reduction between DMPA and danazol, DMPA and COCs (Vercellini et al., 1996) and between DMPA, DNG and GnRH analogues. It was also observed that dysmenorrhoea was significantly worse with danazol and COC in comparison with DMPA after 1 year of treatment (Vercellini et al., 1996). Furthermore, it has been observed that it is possible to treat patients after surgery for endometriosis with progestins and that this results in pain reduction (Vercellini et al., 2003; Cheewadhanaraks et al., 2012).

Additionally, in some countries, subcutaneous DMPA (DMPA-SC 104) is also available at a dose of 104 mg/0.65 ml formulation specifically for subcutaneous injection administered every 3 months. The efficacy and safety of DMPA-SC 104 for the treatment of pain associated with endometriosis for up to 18 months of use was evaluated in two different RCTs (Crosignani et al., 2006; Schlaff et al., 2006). The authors randomized 574 women diagnosed with endometriosis into two groups, DMPA-SC 104 or GnRH (leuprolide), for up to 6 months of treatment, with an evaluation at 12 months after treatment initiation. It was observed in both studies that DMPA-SC 104 and leuprolide were similar in the improvement of at least four of five symptoms associated with endometriosis after 12 months of post-treatment follow-up. One of the strengths of the studies was in improving QoL.

**Progestin-only contraception: etonogestrel-releasing contraceptive implant**

**Pain associated with endometriosis**

Owing to the fact that users of the etonogestrel (ENG)-releasing contraceptive implant had reported less dysmenorrhoea than non-users, one RCT compared the efficacy of ENG implant versus DMPA (150 mg IM) among women with pain-associated endometriosis, dysmenorrhoea, dyspareunia and non-menstrual pelvic pain (Walch et al., 2009).

After 1 year of observation, women from both groups showed improvement in pain intensity and the satisfaction was similar with both treatments. The main limitation of the study was the small sample size (41 women) and the high dropout rate (4 of 21 among ENG implant users and 7 of 20 of DMPA users), mostly due to unpredictable bleeding patterns and no control of dysmenorrhoea.

A summary of the benefits associated with the use of progestin-only contraceptives is reported in Table II.

**Copper intrauterine device**

**Endometrial cancer**

Endometrial cancer is one of the most prevalent cancers in postmenopausal women (Soliman et al., 2005); however, it has also been described in premenopausal women and even in young women (Parslov et al., 2000). Among the risk factors described in premenopausal women are early age at menarche, obesity, nulligravida, polycystic ovary syndrome and amenorrhoea (Parslov et al., 2000; Soliman et al., 2005).

A meta-analysis was conducted to assess the possibility that the use of a copper intrauterine device (Cu-IUD) provides a non-contraceptive benefit of reducing the risk of endometrial cancer (Beining et al., 2008).

Owing to the fact that the LNG-IUS was not yet marketed in the
countries when many of the studies were conducted, the authors assumed that all of studies involved the use of the Cu-IUD. The authors assessed specifically the number of years of exposure and the type of IUD in use. Although the results are conflicting, most of the studies showed a protective effect of the Cu-IUD regarding endometrial cancer (Castellsague et al., 1993; Parazzini et al., 1994; Rosenblatt and Thomas, 1996; Hill et al., 1997; Sturgeon et al., 1997; Benshushan et al., 2002; Beining et al., 2008) [pooled adjusted risk of OR = 0.54, 95% CI 0.47–0.63]. Risk of cervical cancer is also reduced by the Cu–IUD (Castellsague et al., 2011) [OR = 0.55, 95% CI 0.42–0.70].

<table>
<thead>
<tr>
<th>Contraceptive method</th>
<th>Benefits</th>
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<tr>
<td>LNG-IUS</td>
<td>LNG-IUS effectively treats women with heavy menstrual bleeding (Kaulitz et al., 2010; Gupta et al., 2013; Heliovára-Peippo et al., 2013) including users of warfarin (Hale et al., 2010) and improves in quality of life (Peuranpää et al., 2014; Xu et al., 2014). Endometrial hyperplasia is reduced with the use of LNG-IUS (Gallos et al., 2010, 2013b). LNG-IUS reduces the risk of endometrial and ovarian cancer (Soini et al., 2014) and of endometrial polyps in users of tamoxifen (Wong et al., 2013) [HR = 0.19, 95% CI 0.07–0.48]. Pain associated with endometriosis and adenomyosis (Petta et al., 2005; Braghetto et al., 2007; Cho et al., 2008; Tannahasamut et al., 2012) is reduced by LNG-IUS.</td>
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<tr>
<td>DMPA</td>
<td>Pain crisis in sickle cell disease is reduced by DMPA (Abood et al., 1997). DMPA reduces pain associated with endometriosis (Cheewadhanarak et al., 2012).</td>
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<tr>
<td>Etonogestrel implant</td>
<td>Pain associated with endometriosis is reduced by the etonogestrel implant (Wälch et al., 2009).</td>
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<tr>
<td>Cu-IUD</td>
<td>The Cu-IUD reduces the risk of endometrial cancer (Castellsague et al., 1993; Parazzini et al., 1994; Rosenblatt and Thomas, 1996; Hill et al., 1997; Sturgeon et al., 1997; Benshushan et al., 2002; Beining et al., 2008) [pooled adjusted risk of OR = 0.54, 95% CI 0.47–0.63]. Risk of cervical cancer is also reduced by the Cu–IUD (Castellsague et al., 2011) [OR = 0.55, 95% CI 0.42–0.70].</td>
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Table II Summary of benefits associated with the use of progestin-only and intrauterine contraceptives.

LNG-IUS: levonorgestrel-releasing intrauterine system; Cu-IUD: copper intrauterine device; DMPA: depot medroxyprogesterone acetate; RR: relative risk; OR: odds ratio; CI: confidence interval.

A pooled analysis of 26 studies examined the protective effect of an IUD use upon cervical cancer risk (Castellsagué et al., 2011). The authors evaluated whether IUD use may have any influence on cervical human papillomavirus (HPV) infection and consequently the likelihood of evoking cervical cancer. They analysed 2205 cases with cervical cancer and 2214 matched control cases (from the 10 control studies conducted in eight countries); they also analysed 15 272 healthy women from 16 HPV surveys (from 14 countries). The pooled data came from two studies conducted by the International Agency for Research on Cancer and the Institut Català d’Oncologia. The IUD use information was obtained via personal interview.

After adjusting for covariates [cervical HPV DNA and previous Papnicolaou (pap) smears], the authors observed an inverse association between the use of IUDs and cervical cancer (OR = 0.55, 95% CI 0.42–0.70; P < 0.0001), squamous cell carcinoma (OR = 0.56, 95% CI 0.43–0.72; P < 0.0001), adenocarcinoma and adenosquamous carcinoma (OR = 0.46, 95% CI 0.22–0.97; P = 0.035); however, not for women who tested positive for HPV (OR = 0.68, 95% CI 0.44–1.06; P = 0.11). The effect was observed even when the data were stratified by age, years of schooling, marital status, number of screening PapSmears, number of sexual partners, parity (except in nulliparous women), among premenopausal women and in HPV-positive women. However, prior COC use was more common among IUD users. Table II Summary of benefits associated with the use of progestin-only and intrauterine contraceptives.
than among non-IUD users, both in the cases and in the controls. The protective effect of IUD use on cervical cancer risk was not affected by condom use.

The main strengths of the study were the 20,000 women included and the lack of association between cervical HPV infection and years of IUD use. Additionally, the authors did not show that the likelihood of prevalent HPV infection was modified by IUD use, but that it may affect the likelihood of HPV progression to cervical cancer and could act as a protective cofactor in cervical carcinogenesis. However, the mechanism of protection is unclear. It is possible to speculate that the presence of an IUD (mainly a Cu-IUD) and its threads provoke a chronic, non-infectious inflammatory response in the endocervix and cervix, which could modify the course of HPV infection. Also, local inflammation could be provoked during insertion of the IUD and could explain why the protective effect is independent of the length of use. Otherwise, we cannot ignore that during the insertion, the inserter tube and the device may remove cervical pre-lesions that may have already occurred.

One of the limitations of the study is that IUD users habitually visit an HCP to check periodically if the IUD is or is not in situ, and during these visits, the woman may be screened for cervical cancer. This could mean that there is no protective effect from IUD use, but that the protective effect is only due to more intensive cervical screening. However, the authors did not observe any relationship with the number of Pap smears.

**Discussion and Conclusions**

Despite the high contraceptive effectiveness of many contraceptive methods, especially long-acting reversible contraceptives (Winner et al., 2012; Bahamondes et al., 2014), many HCPs, users and potential users are concerned mainly about side effects and safety of many contraceptive methods, both hormonal and non-hormonal, and there is scarce information about many of the considerable benefits that these methods offer beyond contraception. After our review of the evidence, we are able to conclude that many of the hormonal contraceptives and the Cu-IUD available on the market provide many benefits and those without apparent benefits may be because they have not been adequately evaluated. We believe that it is imperative to conduct more research on this matter and generate more reports in the scientific literature and at congresses to disseminate this knowledge. It is imperative to highlight the importance of continuous education to users and potential users through the clinicians and also of continuous education to clinicians regarding the importance of non-contraceptive benefits of the different contraceptive methods.

**Authors’ roles**

L.B., M.V.B. and L.P.S. were responsible for the collection, analysis and interpretation of the information, for writing the first version of this article and for reviewing and approving the final version of the manuscript.

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**Conflict of interest**

L.B. provides lectures for Bayer and Merck and occasionally served on Board of the same companies. L.P.S. provides lectures for Bayer, Teva and Merck and occasionally served on Board of the same companies. M.V.B. declares no conflict of interest.

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non-contraceptive benefits of contraceptive methods


