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Noncontraceptive Uses of Hormonal Contraceptives

More than 80% of U.S. women will use hormonal contraception during their reproductive years (1). Many of these women use hormonal contraception for its noncontraceptive benefits. Hormonal contraceptives can correct menstrual irregularities resulting from oligo-ovulation or anovulation and make menstruation more predictable.

The purpose of this document is to describe noncontraceptive uses for hormonal contraceptives and examine the evidence evaluating the effectiveness of contraceptives for these applications. For many of the conditions, experts suggest that effects of contraceptives are class effects and that all formulations may provide similar therapy. Evidence will be given for specific routes and formulations of hormonal contraception when available, although there are few data on newer methods and formulations.

Background

Patients are often unaware of the noncontraceptive benefits of hormonal contraception, and this represents an opportunity for counseling (2). A brief list of some common noncontraceptive benefits is provided in Box 1.

Most hormonal contraceptives combine a progestin for its contraceptive effects and an estrogen to stabilize the endometrium and reduce unwanted spotting. Users of progestin-only hormonal contraceptives avoid the side effects associated with the use of contraceptives containing estrogen. Progestin-only contraceptives often can be used in women when estrogen is contraindicated; however, unpredictable spotting may be problematic for some patients. Over time, this unwanted bleeding generally subsides and progestin-only methods may provide highly effective long-term contraception.

Since oral contraceptives containing 150 micrograms of mestranol were introduced in 1960, the dose of estrogen per pill has been reduced; currently, pills may con-

Box 1. Potential Noncontraceptive Benefits of Hormonal Contraception

- Menstrual cycle regularity
- Treatment of menorrhagia
- Treatment of dysmenorrhea
- Inducing amenorrhea for lifestyle considerations
- Treatment of premenstrual syndrome
- Prevention of menstrual migraines
- Decrease in risk of endometrial cancer, ovarian cancer, and colorectal cancer
- Treatment of acne or hirsutism
- Improved bone mineral density
- Treatment of bleeding due to leiomyomas
- Treatment of pelvic pain due to endometriosis

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tain as little as 20 micrograms of estrogen. It is unclear whether the trend toward using lower doses of hormonal contraception in the past three decades has reduced any of the noncontraceptive benefits of hormonal contraception.

New progestins with less androgenicity and triphasic preparations designed to reduce overall progestin exposure have resulted in changes to the progestin constituents of the combined oral contraceptive (OC) (3). Other pills contain drospirenone or cyproterone acetate, which have additional antiandrogenic properties.

There is inadequate published evidence to determine whether triphasic combined OCs differ from monophasic combined OCs in effectiveness, bleeding patterns, or discontinuation rates (4). Triphasic preparations have been shown to reduce acne (5), decrease the incidence of ectopic pregnancy, reduce menstrual blood loss, and lower frequency of irregular bleeding and menorrhagia (6). Low-dose and triphasic preparations do not as effectively prevent the development of benign ovarian cysts as did high-dose monophasic preparations (7–9).

The contraceptive patch has comparable efficacy to combined OCs and as such would be expected to reduce ectopic pregnancy, regulate and reduce bleeding, and diminish dysmenorrhea. The extended cycle patch has been used to reduce menstrual cycle-related side effects, including menstrual migraine (10, 11). Also, the contraceptive patch has effects on androgenic markers that compare favorably with combined OCs (12) and, therefore, positive effects on androgenic conditions such as acne should be expected. The contraceptive intravaginal ring is reported to be effective for dysmenorrhea and premenstrual dysphoric disorder (13, 14). There is little published information on the noncontraceptive benefits of progestin contraceptive implants (15). The levonorgestrel intrauterine system is a highly effective contraceptive method with significant noncontraceptive benefits in women with excessive menstrual bleeding and dysmenorrhea. Numerous studies have confirmed the effectiveness of the levonorgestrel intrauterine system for reduction of menstrual blood loss in idiopathic menorrhagia, adenomyosis (16, 17), leiomyomas (18, 19), pain due to endometriosis (20–22), and hemostatic disorders (23) with commensurate reductions in dysmenorrhea and anemia (17, 24).

Clinical Considerations and Recommendations

▶ *Which hormonal contraceptives are beneficial for treatment of dysmenorrhea?*

Dysmenorrhea is pain resulting from intense uterine contractions that are triggered by the release of endometrial prostaglandins. Dysmenorrhea is the most commonly reported menstrual disorder, affecting up to 90% of young women (25). Combined oral contraceptives have been shown to reduce uterine prostaglandin production and to relieve dysmenorrhea in up to 70–80% of women. Small randomized controlled trials (RCTs) (26, 27) and survey data (28) demonstrate a clear reduction in dysmenorrhea among women who use combined OCs. In addition, an RCT comparing the contraceptive intravaginal ring to a combined OC containing 30 micrograms of ethinyl estradiol and 3 mg of drospirenone found reductions in dysmenorrhea in both groups (from 17.4% to 5.9% in the ring group and 19% to 6.4% in the combined OC group) (13).

The single-rod contraceptive progestin implant also appears to reduce dysmenorrhea in most users (29). One study reported a decrease in the number of women with dysmenorrhea from 59% at baseline to 21% after treatment (30). Of those women who reported a history of dysmenorrhea at baseline, 81% showed improvement with progestin contraceptive implant use. Another study reported a 35% incidence of dysmenorrhea among participants at baseline, with 82% of these women reporting improvement in symptoms after progestin contraceptive implant use (31). Data on the effects of the levonorgestrel intrauterine system for dysmenorrhea are limited, but given that this device reduces or eliminates menstruation for many women, the positive benefits reported seem consistent with the mechanism of action (32).

Limited data suggest that combined OCs can reduce the severity of dysmenorrhea in women with endometriosis (33). Continuous combined OCs may offer additional benefit by elimination of menstruation and associated dysmenorrhea. Both depot medroxyprogesterone acetate (DMPA) and the progestin contraceptive implant have been shown to reduce pain due to endometriosis (34, 35). Several trials have demonstrated the efficacy of the levonorgestrel intrauterine system in treating dysmenorrhea and chronic pelvic pain associated with endometriosis (20, 21, 36, 37).

▶ *Which hormonal contraceptives are beneficial for cycle control?*

Combined hormonal contraceptives can correct menstrual irregularities resulting from oligo-ovulation or anovulation and make menstruation more predictable. Extended cycle regimens, including 84-day continuous combined OC followed by a 7-day hormone-free interval, can further reduce scheduled bleeding associated with hormonal contraceptives but may be associated with higher rates of spotting and other unscheduled bleeding in the first months of therapy (38).

Most clinical trials have demonstrated that unscheduled spotting or light bleeding is common in the first 3–6 months with all combined OCs. Women using hormonal contraception for menstrual regulation should be counseled about this possible effect.

The progestin-only pill is thought to inhibit ovulation in approximately 50% of women (39, 40). The remainder of women using this method will continue to menstruate regularly. Other progestin-only methods (DMPA and levonorgestrel intrauterine system) initially result in increased rates of unscheduled bleeding but lead to diminished blood loss over time as a substantial number of women using these methods become amenorrheic.

Evaluation of a continuous daily regimen of 90 micrograms of levonorgestrel per 20 micrograms of ethinyl estradiol demonstrated that 79% reported absence of bleeding by pack 13 with the incidence of breakthrough bleeding decreasing progressively from initiation (41). Several pills also are available that extend the active pills to 24 days (1 mg of norethindrone acetate per 20 micrograms of ethinyl estradiol followed by four placebo pills and 3 mg of drospirenone per 20 micrograms of ethinyl estradiol followed by four placebo pills). The drospirenone-containing pill has been shown in a randomized trial to reduce the symptoms of premenstrual syndrome (42), and it has been approved by the U.S. Food and Drug Administration for treatment of premenstrual dysphoric disorder and acne.

Women on cyclic hormonal contraception may experience premenstrual symptoms as well as distressing symptoms (including pelvic pain, headaches, breast tenderness, and bloating) in the hormone-free interval (38, 43). Extending the usual 21-day cycle of contraceptive pills (41, 44, 45) was shown to reduce pelvic pain and headaches while improving overall mood (46). Extended use of the contraceptive patch (10) and the contraceptive ring (47) affords similar benefits. Such regimens are one way to avoid menstrual-related symptoms or to delay menstruation for women who anticipate inconvenient menstrual bleeding during travel or important life events.

A progestin injection (DMPA) or progestin contraceptive implant would not be ideal for short-term induction of amenorrhea because of the unpredictable bleeding associated with early use. A substantial number of women using the levonorgestrel intrauterine system and DMPA will achieve amenorrhea. These methods could be considered for long-term menstrual suppression if immediate amenorrhea is not desired, if there is a contraindication to an estrogen containing contraceptive, or if long-term contraception is desired.

▶ *What is the evidence supporting hormonal contraceptive use as an alternative to surgical therapy for menorrhagia?*

Excessive menstrual bleeding (60–80 mL per cycle or greater) if untreated can lead to iron deficiency anemia (48). It has been estimated to occur in approximately 10% of women of reproductive age, although as many as 30% of women will seek treatment for this condition (48–50). Combined hormonal contraceptives can reduce excessive menstrual bleeding in most affected women and are considered a reasonable option for initial management of menorrhagia. This is particularly true in women who may desire future fertility because the contraceptive effect is readily reversible.

Menstrual blood loss is reduced by 40–50% in women who used cyclic combined OCs (51–53). The effectiveness of combined OCs may be enhanced by extended cycle or continuous therapies that reduce the number of total bleeding episodes (54, 55). Extended cycle and continuous combined OCs as well as many of the progestin-only contraceptive options (progestin-only pills, DMPA, progestin contraceptive implants, and levonorgestrel intrauterine system) reduce overall bleeding days and may achieve amenorrhea in many women (45, 56). Clinical trials with the single-rod progestin contraceptive implant have demonstrated that the irregular bleeding typical of progestin-only methods occurs in the first 3 months, with amenorrhea resulting in 30% and 40% of women at 1 year (29, 57). Reductions in blood loss of up to 86% after 3 months and up to 97% after 12 months of use have been reported with the levonorgestrel intrauterine system (58–61). At 12 months after insertion of the levonorgestrel intrauterine system, reported rates of amenorrhea vary between 20% and 80% (62–65).

A Cochrane review examined the effectiveness of the levonorgestrel intrauterine system compared with oral cyclical norethindrone for treatment of heavy menstrual bleeding (66). The report concluded that the levonorgestrel intrauterine system is a more effective treatment, and that women with a levonorgestrel intrauterine system are more satisfied and willing to continue with treatment. However, these women do experience more side effects, such as intermenstrual bleeding and breast tenderness. A systematic review and meta-analysis found that both the levonorgestrel intrauterine system and endometrial ablation were associated with similar reductions in menstrual blood loss up to 24 months, and both treatments were generally associated with similar improvements in quality of life (67). Progestogenic side effects were greater in women using the levonorgestrel intrauterine system, and serious side effects occurred more often in those receiving surgical intervention (66, 68).

Markov modeling has been used to estimate the cost-effectiveness of different approaches to management of menorrhagia in women desiring contraception (69). In the absence of a pathological cause, the use of a combined OC for menorrhagia was the most cost-effective approach in the first year only. In women who responded initially to a combined OC, it was more cost-effective to switch to a levonorgestrel device than to continue with combined OCs. In women who failed to respond to combined OCs, the levonorgestrel intrauterine system was the most cost-effective approach followed by surgery if the levonorgestrel intrauterine system also failed (69).

▶ *Which hormonal contraceptives are beneficial for treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder?*

The first systematic studies to examine the effects of combined OCs on PMS found little difference in PMS symptoms between combined OC users and nonusers (70, 71). In addition, there were no significant differences between agents with differing progestational potencies (72). Monophasic and triphasic preparations showed similar rates of symptomatology (73).

Premenstrual dysphoric disorder, a severe form of PMS, is a condition that adversely affects the psychologic well-being and social interactions of some 3–5% of women of reproductive age (74). The only RCTs to demonstrate improvement in symptoms of premenstrual dysphoric disorder have involved a combined OC with a 24/4 regimen containing 30 micrograms of ethinyl estradiol with drospirenone as the progestogenic component (42, 75, 76). These trials have been shown to offer relief from both physical and psychologic manifestations of premenstrual dysphoric disorder with improvement in health-related quality of life.

A direct comparison of a drospirenone containing combined OC with the intravaginal contraceptive ring reported equivalent improvement in PMS (13). Combined OCs containing 30 micrograms of ethinyl estradiol with 3 mg of drospirenone also have been shown to decrease premenstrual mood deterioration in reproductive-aged women receiving treatment for depression (77). Another approach that appears to be helpful for PMS is to suppress menstruation and stabilize hormones with extended cycle or continuous combined OC regimens (78).

▶ *Which hormonal contraceptives are beneficial for treatment of menstrual migraines?*

Sixty percent of women with migraines link attacks to menstruation. Documented menstrual migraine occurs in 8–14% of women (79–81). These migraines are experienced exclusively at the time of menstruation and these women are virtually free of migraine at other times of the cycle, with the exception of the small percentage of women who experience a brief exacerbation associated with ovulation. The use of extended cycle or continuous hormonal contraception (including combined OCs, the patch, and DMPA) reduces or eliminates the hormonal fluctuations thought to precipitate migraine attacks and thereby may afford relief of migraine headaches for some women (11, 79, 82).

Although cerebrovascular events occur rarely among women with migraines who use combined OCs, the impact of a stroke is so devastating that clinicians should consider progestin-only, intrauterine, or barrier contraceptives for women who experience migraine with focal neurological signs, or those who smoke or who are 35 years or older.

▶ *Which hormonal contraceptives are effective for treatment of hirsutism and acne?*

All combined OCs have the potential to improve hirsutism and acne because they all increase sex hormone binding globulin and suppress luteinizing hormone-driven ovarian androgen production, thereby reducing the levels of free androgen, which initiate and maintain the acne and hair growth. Although hormonal therapy can prevent an increase in hirsutism, existing hair will need to be permanently removed.

In a small RCT, a drospirenone and ethinyl estradiol combination was as effective as cyproterone acetate combined with ethinyl estradiol in improving hirsutism (83). Another small RCT compared second generation combined OCs containing levonorgestrel with third generation combined OCs containing desogestrel. This trial found that both formulations were effective in improving hirsutism (84).

A Cochrane review evaluated 23 trials on the effects of combined OCs on acne: 5 placebo-controlled trials, 17 trials comparing different combined OC regimens, and 1 trial comparing a combined OC to an antibiotic (85). Combined OCs reduced both inflammatory and noninflammatory facial acne lesions as determined by acne lesion counts, severity grades, and self-assessed acne compared with placebo. Few differences were found between type of OCs and effectiveness for acne treatment. Differences in the comparative effectiveness of combined OCs containing varying progestin types and dosages were less clear although combined OCs containing antiandrogenic progestins (drospirenone or cyproterone acetate) were superior in some comparative trials.

Hormonal contraceptive methods that bypass the first-pass liver effects of the OC (the contraceptive patch and the vaginal contraceptive ring) may have a lesser effect on sex hormone binding globulin. Progestin-only methods are not normally considered effective for acne.

▶ *What is the role of hormonal contraceptives in decreasing cancer risk?*

Endometrial Cancer

Strong epidemiological evidence supports a 50% reduction in the risk of endometrial cancer among women who have used combined OCs compared with women who have never used combined OCs (86–91). The Cancer and Steroid Hormone Study confirmed that both short-term (less than 5 years) and long-term (equal to or greater than 5 years) use of combined OCs resulted in similar reductions in risk (92). Longer durations of use were associated with greater decreases in risk to as low as an odds ratio of 0.2 (93, 94). This effect lasts for up to 20 years (95). Overall deaths from endometrial cancer were significantly reduced in past OC users (HR 0.2) (96). Limited data suggest that risk reduction persists with new formulations and lower dose combined OCs (90). Some studies have found a reduction in endometrial cancer regardless of the progestin potency of the combined OC (97) whereas others found a greater risk reduction in those combined OCs with highest progestin potency (88, 98). Depot medroxyprogesterone acetate shows a similar protective effect on subsequent development of endometrial cancer (99, 100).

The levonorgestrel intrauterine system achieves concentrations in the endometrium several hundred-fold higher than achieved with traditional systemic therapy (101). The levonorgestrel intrauterine system is now approved as the progestin component of postmenopausal hormone therapy in some countries (102). Accordingly, investigators have examined its use for medical treatment of endometrial hyperplasia (103–105). A systematic review found the levonorgestrel intrauterine system to be an effective treatment for hyperplasia without atypia (regression in 96%) (106). However, accurate diagnosis and ongoing surveillance are essential. For women with hyperplasia with atypia, data on the effect of the levonorgestrel intrauterine system are limited to small case series. Therefore, it is unclear whether the levonorgestrel intrauterine system is effective for treatment of atypical hyperplasia. All investigators have emphasized the importance of continuing endometrial surveillance to detect cases where atypical hyperplasia persists or progresses. Reports of endometrial cancer developing despite use of the levonorgestrel intrauterine system suggest the need for caution with this approach (107). Endometrial sampling can never ensure that the most advanced disease is identified, and the risk of missed endometrial adenocarcinoma is significant (108). The levonorgestrel intrauterine system also has been shown to protect the endometrium in women taking tamoxifen for adjuvant breast cancer therapy (109).

Ovarian Cancer

A collaborative reanalysis of worldwide data on combined OCs and ovarian cancer involving 45 epidemiological studies with 23,000 ovarian cancer cases and 87,000 controls has demonstrated that every use of combined OC decreases the risk of ovarian cancer by 27% (110). The longer the duration of combined OC use, the greater the risk reduction, amounting to a decrease of approximately 20% for every 5 years of use. The protective effect has been shown to extend to low-dose pills (111). Some have suggested that combined OCs be used as a form of chemoprotection against ovarian cancer by women with *BRCA* gene mutations (112).

Colorectal Cancer

A meta-analysis of 6 cohort and 14 case–control studies reported an 18% reduction in the risk of developing colorectal cancer among OC users. This reduction was greatest for recent use and showed no duration effect (113). The Royal College of General Practitioners' Oral Contraception Study also suggested that current or recent, but not past, use of combined OCs conferred a lower risk of colorectal cancer, although none of the findings reached statistical significance (114).

▶ *Can hormonal contraceptives prevent or be used to treat ovarian cysts?*

By preventing ovulation, hormonal contraception should reduce the findings of follicular and corpus luteal cysts on ultrasound examination as suggested by the results of small case series reports (115). Such cysts are rarely of clinical significance although they may lead to unnecessary repeat ultrasound studies when discovered incidentally. Not all follicular activity is suppressed with low-dose OCs, and small ovarian cysts are common in users of these formulations (7–9). Case–control studies have failed to demonstrate a difference in the rate of detection of functional ovarian cysts in women using either monophasic or triphasic combined OCs (116).

The follicle-stimulating hormone-induced suppression of hormonal contraceptives would seem to be an ideal way to accelerate the spontaneous regression of larger functional ovarian cysts. However, available research does not support this notion. In a series of RCTs in women of reproductive age, the use of combined OCs did not hasten the resolution of functional ovarian cysts compared with expectant management (117–120). Therefore combined OCs should not be used to treat existing functional ovarian cysts.

Older studies demonstrated that asymptomatic unruptured follicular cysts may occur in 10–20% of cycles in women using progestin-only pills (121). Users of progestin contraceptive implants, although anovulatory,

may experience formation of ovarian cysts (122). Most of these cysts are asymptomatic and resolve spontaneously.

▶ *Do hormonal contraceptives have an effect on bone mass and fracture risk?*

Estrogen is a powerful inhibitor of bone resorption. Because fractures related to fragile bone occur infrequently in young women, surrogate markers such as bone mineral density (BMD) are often used to evaluate the effects of hormonal contraception on bone. However, BMD provides information on only one facet of bone health, and its use to predict future fracture risk in young hormonal contraceptive users has not been validated (123).

Oral contraceptives have been reported to have beneficial effects or no effect on BMD (124–128). Combined OC use is associated with increased bone density among women in the later reproductive years, with longer duration of use (greater than 10 years) being associated with greater BMD (124, 125, 129, 130). It has been suggested that combined OC use at times of estrogen deficiency may reduce subsequent fracture risk (131). Although one systematic review concluded that there was fair evidence that combined OCs increased BMD, other data led to the conclusion that adolescent and young adult women who use combined OC will have lower BMD than nonusers (132–134). Higher calcium intake may provide protection in this circumstance (135). Combined OC use in perimenopausal and postmenopausal women preserved bone mass, whereas nonusers lost BMD (131).

A Cochrane review examined the effect of hormonal contraception on fracture risk and found no RCTs examining fracture as an outcome (136). They reported on three observational studies that found no effect of combined OCs on risk of fracture (137–139), three studies with a significantly increased risk of fracture among combined OC users (140–142), and three studies reporting a protective effect for combined OC use (143–145). Most of the studies did not specify the formulation of the combined OCs, and none provided results specifically for users of low-dose formulations.

They also concluded from a range of studies examining the effects of combined OCs on BMD that combined OCs did not appear to affect BMD or biochemical markers of bone turnover (136). The evidence for other combined hormonal methods is limited, with one study suggesting that BMD is lower among premenopausal users of etonogestrel and ethinyl estradioal vaginal rings than in nonusers (134). Because the BMD was within one standard deviation of the untreated controls, this result was felt to lack clinical significance (146).

Several studies have found decreased BMD in users of DMPA and progestin implants (147–149). Additional data raise concern that DMPA followed by low-dose OC pill use (20 micrograms of ethinyl estradiol) may slow bone recovery (150). Bone loss during contraceptive use may be analogous to that which occurs with breastfeeding and is rapidly recovered (151, 152). Past users of DMPA, including women who used DMPA after 40 years of age show similar BMD to that in women who never used DMPA (153). No data exist on fracture risk among postmenopausal women who previously used DMPA.

▶ *Does combined OC use affect the development of leiomyomas? Is there a role for combined OCs or levonorgestrel intrauterine systems in the treatment of leiomyomas?*

The precise effects of combined OCs on the formation and growth of uterine leiomyomas remain poorly understood. Case–control studies have reported no effect (154) or reduced risk (155, 156) of leiomyomas among combined OC users. Two large cohort studies found that neither current nor past combined OC use was associated with the risk of developing leiomyomas (157, 158).

Data are limited about the effects of estrogen and progestin treatment of leiomyomas. Estrogen and progestin treatment may control bleeding symptoms without stimulating further leiomyoma growth. However, studies of progestin therapy have demonstrated mixed results. Although several small studies have shown a decrease in leiomyoma size during progestin therapy, other studies using progestin therapy alone or in conjunction with a gonadotropin-releasing hormone agonist identify an increase in leiomyoma volume or uterine volume during therapy (159). The levonorgestrel intrauterine system has been shown to reduce overall uterine volume with little or no effect on the size of leiomyomas (32, 160).

Based on the limited data available it appears overall that combined OCs and the levonorgestrel intrauterine system have little effect on the development of uterine leiomyomas (18).

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- Combined OCs should not be used to treat existing functional ovarian cysts.
- Use of combined hormonal contraception has been shown to decrease the risk of endometrial and ovarian cancer.

- Combined OCs have been shown to regulate and reduce menstrual bleeding, treat dysmenorrhea, reduce premenstrual dysphoric disorder symptoms, and ameliorate acne.
- Continuous combined hormonal contraception, DMPA, and the levonorgestrel intrauterine system may be considered for long-term menstrual suppression.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Based on the limited data available it appears overall that combined OCs do not increase the risk of development of uterine leiomyomas.
- Hormonal contraception should be considered for the treatment of menorrhagia in women who may desire further pregnancies.

Proposed Performance Measure

Percentage of women using hormonal contraception for symptomatic relief of menorrhagia or dysmenorrhea or both who have no contraindications and wish to preserve reproductive function

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1995 and November 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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