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REVIEW ARTICLE

No-daily hormonal contraception today: general overview and application in specific clinical settings

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ABSTRACT

No-daily hormonal contraception includes short-acting reversible contraceptives (SARC), which contain estrogen and progestin (vaginal ring and transdermal patch), and long-acting reversible contraceptives (LARC), which contain only progestin (levonorgestrel-releasing intrauterine device and etonogestrel subdermal implant). No-daily hormonal contraceptives are reversible, avoid oral daily intake and have high contraceptive efficacy. They offer advantages over the traditional oral route, increasing user compliance, and reducing forgetfulness. Furthermore, they have several non-contraceptive benefits. This review aims to highlight the strengths of choices other than the traditional 'pill', with the goal of implementing contraceptive counseling, which should be personalized and tailored to each woman. Different subsets of patients may use no-daily contraception at different stages of their lives, with the option of either LARC or SARC. Specific contexts for its use are adolescence, perimenopause, obese women, eating disorders or intestinal malabsorption, breastfeeding, and post voluntary termination of pregnancy. Non-daily contraceptives can be an attractive alternative to the daily contraceptive pill, with benefits that are relevant to each woman desiring contraception, especially in unique and specific settings where customization of the contraceptive method is essential.

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No-daily hormonal contraception; short-acting reversible contraceptives (SARC); contraceptive vaginal ring; contraceptive transdermal patch; hormonal long-acting reversible contraceptives (LARC); levonorgestrel-releasing intrauterine device (LNG-IUD); etonogestrel (ETN) subdermal implant

Introduction

The use of modern contraceptive methods in women of reproductive age is extremely heterogeneous around the world, ranging from 3.7% in Albania to 81.6% in Finland. Overall, 45.2% of contraceptive users rely on permanent or long-acting methods [i.e. female and male sterilization, intrauterine devices (IUD), subdermal implants], 46.1% on short-acting methods [such as male condoms, oral contraceptive pills (OC), injectables, and other modern methods), and 8.7% on traditional methods (withdrawal, rhythm methods, and others] [1].

Adherence to a specific method of contraception, defined as the proportion of women or cycles with self reported correct use of the assigned device, is the result of all those elements contributing to its selection and is the key factor of effectiveness in real life [2]. Moreover, it correlates strictly to acceptability in terms of side effects and appreciation of possible extra-contraceptive benefits for general and reproductive health, as well as for quality of life.

No-daily hormonal contraception today represents a step forward in favoring adherence and long-acting reversible contraception (LARC), which only contain progestins (levonorgestrel-releasing intrauterine device (LNG-IUD) and etonogestrel (ETN) subdermal implant), seems to be the most reasonable choice for this purpose [3]. However, it contains only progestins and is not suitable for all women that prefer having control of their used methods or do not accept the eventual unpredictable bleeding profile. Moreover, some women prefer or need to assume estrogens in combination [4] and they can achieve this goal by using short-acting reversible contraception (SARC) including weekly patches or monthly vaginal rings [2]. No-daily methods have been on the market for several years, but the value of selecting one method or another in women's lives has not yet been fully elucidated.

This narrative review brings together the evidence on the most widely available no-daily contraceptive technologies, broadening the horizon of their use in clinical practice. Our scope is to highlight the strengths of choices other than the traditional 'pill', with the ultimate goal of implementing contraceptive counseling, which should be personalized and tailored to each individual woman.

Materials and methods

Search strategy and selection criteria

We searched PubMed using the following keywords: contraceptive AND transdermal AND patch; contraceptive AND vaginal AND ring; hormonal AND 'long-acting' AND reversible AND

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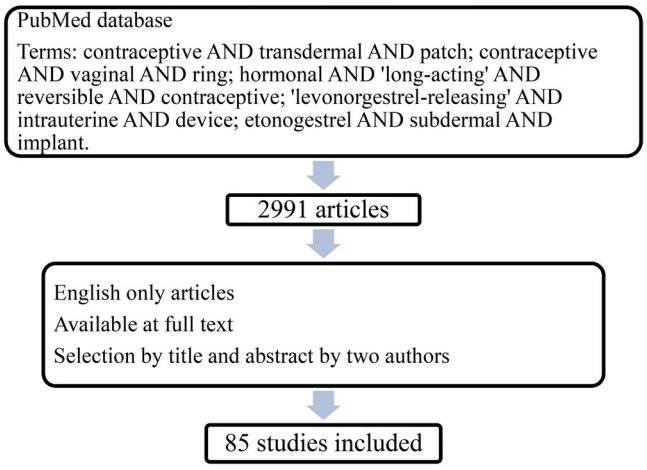

Figure 1. Flow chart regarding the selection process of the studies used in the review.

contraceptive; 'levonorgestrel-releasing' AND intrauterine AND device; etonogestrel AND subdermal AND implant. The search was conducted on November 18, 2022.

Only the publications written in English were considered and a selection was made by title and abstract; original papers selected for inclusion were independently reviewed by two of us (VB and SA) (Figure 1). When there were conflicts in the selection of the studies, the impact factor of the journal was evaluated, and priority was given to higher quality, more recent, and more prestigious journals.

Discussion

No-daily hormonal contraceptives include methods that do not involve taking a contraceptive preparation daily; nevertheless guarantee a return to fertility when discontinued. This category of contraceptives includes no-daily SARC, containing estrogens and progestin (vaginal ring and transdermal patch), and LARC, which are no-daily by definition and contain only progestins (levonorgestrel-releasing intrauterine system (LNG-IUD) and etonogestrel (ETN) subdermal implant) (Table1). Medroxyprogesterone acetate (MPA) intramuscular or subdermal injections use as a contraceptive is off-label in many countries, while it is used for the palliative therapy of metastatic and inoperable endometrial cancer and advanced stage hormone-dependent breast cancer [5]. Other types of injectables and implants, such as 5 years LNG implants, are less common and registered in a few countries. Therefore, those methods will not be considered in this review.

No-daily hormonal contraceptives have high contraceptive efficacy [6], and they are reversible. They offer advantages over the traditional oral route, avoiding the need for daily pill intake of combined OC (COC), increasing user compliance, and reducing forgetfulness [2]. Furthermore, they have non-contraceptive benefits, such as reducing dysmenorrhea, menstrual bleeding, and premenstrual syndrome [7, 8].

Table 1. No daily hormonal contraceptives. SARC: short-acting reversible contraceptives; LARC: long-acting reversible contraceptives; LNG-IUD: levonorgestrel-releasing intrauterine system; ETN etonogestrel; EE: ethinylestradiol; LNG: levonorgestrel.

No-daily contraceptives			
Category	**Type of Hormones**	**Contraceptive option**	
No-daily SARC	Progestins + estrogens	Vaginal ring	ETN + EE
		Transdermal patch	Norelgestromin + EE
LARC	Progestins	LNG-IUD	LNG
		ETN subdermal implant	ETN

No-daily short-acting reversible contraceptives (SARC)

Among SARC, no daily formulations include the vaginal ring and the transdermal patch. They act by inhibiting ovulation and by modulating the composition of cervical mucus [9]. Their contraceptive effectiveness and failure rates are similar to those of COC [6].

These methods allow monthly menstrual flow, a rapid return to fertility after discontinuation, and good acceptability due to their non-invasiveness (Tables 2 and 3).

Bypassing the gastrointestinal tract, the ring and the patch allow avoiding the first-pass effect and, therefore, drug bioavailability is higher. This allows good efficacy even in women with gastrointestinal malabsorption [10]. Increased bioavailability, along with the ability to provide a sustained drug release rate, allows using lower doses. The decreased dosage could improve cycle control while reducing side effects. However, the presence of ethinylestradiol (EE) makes these formulations unsuitable during breastfeeding or in patients with contraindications to estrogens [11].

Vaginal ring

The vaginal route is an ideal method of drug administration, and the advantages of this method are well-established [12]. The ring matrix releases on average daily doses of 15 µg of EE and 120 µg of ETN over 3 weeks [13–15]. According to a Cochrane review, ring users appear more satisfied with their method than COC users and contraceptive effectiveness is not different for the vaginal ring in comparison to COC [2]. It appears that vaginal ring users are less likely to discontinue (overall or due to adverse events) than COC users [16,17].

Table 2. Pros and cons of no-daily SARC. SARC: short-acting reversible contraceptives; EE: ethinylestradiol.

No-daily SARC	
PROS	Avoidance of the first hepatic passage → low and constant blood levels of EE → fewer side effects and excellent cycle control
	Effective also in intestinal malabsorption
	Monthly menstrual flow
	Rapid return to fertility
	Non-invasiveness with good acceptability
	Containing EE
CONS	User-dependent contraceptives
	Monthly menstrual flow
	EE → not for use if contraindications are present (i.e. breastfeeding)
	EE → increased risk of thromboembolism

Table 3. Pros and cons of LARC hormonal contraceptives.

No-daily LARC	
PROS	Maximum contraceptive efficacy
	Do not require any user action after insertion
	The user cannot alter the method's efficacy
	Ideal for patients with low compliance (adolescents or patients with disabilities) or to avoid forgetfulness ('forgettable contraception')
	Long-term but reversible contraception
	Progestin-only → if estrogens are contraindicated and in perimenopause
	Possible use during breastfeeding
	Do not increase thromboembolic risk
	Effective for dysmenorrhea and endometriosis
CONS	High upfront cost
	Dependent on the correct placement
	Possible menstrual irregularities

Fewer adverse effects may be related to steady-state hormone levels, in contrast to the hormonal peaks achieved with COC [2]. Results from a study that compared the pharmacokinetics of EE released from three hormonal contraceptive methods using the vaginal, transdermal, and oral route of administration, show that for vaginal ring users, exposure to EE is on average 3.4 times lower than for those who use the transdermal patch and approximately twice as low as those who use the COCs. Of the three contraceptive methods, exposure to EE is the lowest for the ring group, and subjects using vaginal rings have the least variation in EE serum levels [11].

The rate of breakthrough bleeding and spotting is lower than with COC. Nausea and acne appear less likely among ring users compared to the COC group [2].

According to a randomized study by Stewart et al. [18], vaginal ring users appear less likely than COC users to report increased body weight, headaches, negative mood impact, or sex drive.

Data suggest that biofilm formation on the vaginal ring does not alter the vaginal microbiome or impact mucosal host defense; on the contrary, vaginal ring-releasing hormones may be important for the protection of the vaginal microbiota [19]. As part of a prospective comparative study in asymptomatic women starting contraception, De Seta et al. reported that women who use the vaginal ring show a significant increase in the number of lactobacilli in the vaginal flora compared to both baseline and COC users [20]. This is most likely attributed to the action of the EE on vaginal flora composition [21,22].

EE enhances procoagulant factors, such as factor VIIa and fibrinogen, and decreases the activity of anticoagulation mechanisms. The acquired hypercoagulability seems to be independent of the route, but directly dependent on the dose of EE [23]. Although EE is present in the vaginal ring, the daily doses of EE (15 µg) are lower than in most pills.

In a randomized study by Duijkers et al. [24] vaginal ring users show a lower mean area under the curve for insulin compared to the COC group with LNG. Similarly, in a prospective randomized study of young, healthy, lean women in need of hormonal contraception, vaginal ring use does not impair insulin sensitivity as compared with COC use [25].

However, two other studies [26,27] showed no significant differences in the carbohydrate metabolism measures for the ring users. The evidence regarding the action on insulin sensitivity is therefore not yet conclusive.

Transdermal patch

The transdermal patch is a weekly combined contraceptive method designed to deliver 20 µg of EE and 150 µg of norelgestromin daily. It does not differ significantly in contraceptive effectiveness compared to COC [2].

In the study that compared the pharmacokinetics of EE released from three hormonal contraceptive methods, the patch was found to produce EE serum levels higher than those expected with a COC containing 30 mcg of EE. The transdermal patch maintains a steadier level of serum estrogen than COC, however, the area under the curve is higher for patch users [10]. For this reason, the US Food and Drug Administration (FDA) warns that women using the patch may be exposed to more estrogen on average than women taking a pill with EE 35 µg [28].

Exposure to EE following transdermal patch application has been compared for different sites; absorption is approximately 20% less when the patch is worn on the abdomen compared with the arm, buttock, or torso based on serum concentrations, although mean serum concentrations are still within reference ranges [29].

Breakthrough bleeding and spotting are less common within the patch group than in the COC group, and patch users appear more likely to be very satisfied with their method than COC users [30].

Although patch users show better adherence per cycle than COC users, more patch users discontinue early than COC users [2]. Patch users are more likely to discontinue due to adverse events since they report breast discomfort or pain, nausea, vomiting, and dysmenorrhea more often compared to COC.

A systematic review [31] identified conflicting evidence from 7 observational studies that compared the venous thromboembolic (VTE) risk associated with the use of the transdermal patch to that with the use of COC containing LNG or norgestimate. One retrospective cohort study [32] and one case-control study [33] report significant, 2-fold greater VTE risk among transdermal patch users compared to COC users [34].

Long-acting reversible hormonal contraceptives (LARC)

LARC are contraceptive methods approved for consecutive use for 3 to 5 years. They include the Levonorgestrel-releasing intrauterine system (LNG-IUD), and the ETN subdermal implant.

Many studies have demonstrated that LARC methods are more effective than SARC [3,33] since there is no difference between typical and perfect use [5]. These contraceptive methods do not require any user action after insertion and the user cannnot alter the method's efficacy [3]. For this reason, LARC are defined as 'forgettable contraceptives' [35], being suitable for the categories of patients for which behavior-related variables may affect compliance (disabled people, adolescents, or those who tend to forget) [3,36,37].

These devices also have high continuation rates: in the CHOICE Project continuation rates for participants who chose LARC methods were higher than for those who chose SARC contraceptives [38]. The effectiveness of LARC methods is comparable to that of female sterilization and is independent of age, parity, or body mass index (BMI) [3], but allows return to fertility.

Since hormonal LARC exclusively release progestin substances, they do not increase the risk of VTE and can be used in most of the patients for which estrogens are contraindicated [39].

Multiple factors, including the high upfront cost, are responsible for the low use of LARC [3]. However, durability of the contraceptive method amortizes costs. LARC appears to become cost-neutral within 3 years of initiation when compared with SARC contraception [40]. Moreover, LARCs, having a very good effectiveness, can be considered cost-effective since they avoid pregnancies and all direct and indirect costs associated to them.

Abnormal uterine bleeding is the main cause of the early discontinuation of LARC. Counseling and anticipatory guidance are important and can help prevent early removals [3].

Intrauterine contraception (IUC)

Complications with IUC are uncommon and include expulsion (2–10% during the first year) [5], method failure, and uterine perforation (a rare event, occurring in 1.4 per 1,000 LNG-IUD insertions) [41].

The use of the IUC does not increase the absolute risk of ectopic pregnancy, since IUC effectively prevents pregnancy; however, if pregnancy does occur with an IUC in place, it is more likely to be ectopic [42].

Studies that examined women who were diagnosed with pelvic inflammatory disease (PID) after IUC insertion found mixed results. The study with the largest sample size found a greater incidence of PID in the first 20 days after insertion. IUC usage represents an unacceptable health risk in women with puerperal sepsis, immediate post-septic abortion, uterine fibrosis with distortion of the uterine cavity, and persistently elevated β- Human

Chorionic Gonadotropin (hCG) levels or malignant disease [42]. The same is true also if it is initiated in women presenting unexplained vaginal bleeding, cervical cancer awaiting treatment, endometrial cancer, current PID, and current purulent cervicitis or chlamydial infection or gonorrhea [43].

Levonorgestrel releasing intrauterine system (LNG-IUD). Different LNG-IUD are available containing various doses of LNG. LNG-IUD FDA-approved up to 8 years of consecutive use can contain 52 mg of LNG (releasing 20 mcg per day) or 19.5 mg (13 mcg/day). LNG- IUD containing 13.5 mg of LNG (8 mcg/day) is FDA-approved only for 3 years of consecutive use [41].

The mechanism of action of LNG-IUD is primarily the thickening of cervical mucus, impaired sperm penetration [3], and massive decidual changes in the endometrium [44]. Bleeding patterns are similar when comparing different dosages of LNG-IUD, with a marked reduction in the number of bleeding/spotting days after the initial 3 months of use and continuing to decline thereafter [45]. LNG-IUD is more effective in reducing heavy menstrual bleeding than COC [46]. The LNG-IUD may control abnormal uterine bleeding as well as uterine volume in adenomyosis and fibroids, in these subsets of patients LNG-IUD can determine the decrease of uterine volume [47]. In women with idiopathic heavy menstrual bleeding, the LNG-IUD reduces menstrual blood loss more effectively and has a higher likelihood of treatment success than oral medroxyprogesterone acetate [48].

The 19.5 mg and the 13.5 mg LNG-IUD are considered low-dose LNG-IUD. They have smaller T-frames (28 × 30 mm vs 32 × 32 mm) and smaller hormone reservoirs, allowing them to be placed using a smaller diameter placement tube [49]. In a randomized, open-label, three-arm, phase II study by Gemzell-Danielsson et al. [45] studying the efficacy, bleeding profile, and safety of two low-dose and one high-dose LNG-IUD, it appears that 98.5% of successful placements were achieved at the first attempt. The placement was rated as "easy" for 94% of subjects in the low-dose group compared with 86.2% of subjects in the high-dose group. In a participant-blinded randomized trial on 318 adolescents, the pain level was significantly higher after the levonorgestrel 52-mg IUD placement, than the levonorgestrel 19.5-mg IUD, and the levonorgestrel 19.5-mg IUD placemat was easier when compared with the levonorgestrel 52-mg IUD [50].

Most women who use a low-dose LNG-IUD continue to ovulate [42].

Although the LNG-IUD releases only a small amount of steroid, some women may experience hormone-related effects, such as headaches, nausea, breast tenderness, mood changes, and ovarian cyst formation. The drug-related adverse event that occurs more frequently with 52 mg LNG-IUD is ovarian cyst (> 3 cm) formation, caused by persistent ovarian follicles and generally resolving spontaneously [45,51]. The 52-mg LNG-IUD is used to treat menstrual-related disorders such as menorrhagia and dysmenorrhea, and atypical endometrial hyperplasia [52].

LNG-IUD appears to be a safe and effective contraceptive method for obese women. The system is not associated with an increased risk of VTE and exerts only minimal effects on plasma lipids and glucose metabolism. An advantage might also be the protection of the endometrium in obese women [51].

Contraceptive implants

Progestogen-releasing contraceptive implants are placed subdermally. The ETN subdermal implant is radio-opaque and is easily visualized on X-rays [42]. It consists of an ethylene-vinyl acetate copolymer core that contains 68 mg of ETN surrounded by an ethylene-vinyl acetate copolymer skin and it is approved for use for up to 3 years [53].

The primary mechanism of action of the ETN subdermal implant is suppression of ovulation, additional contraceptive efficacy may be conferred by thickening cervical mucus [42].

The ETN subdermal implant is the most effective method of reversible contraception, with a typical-use pregnancy rate of 0.05% [5]. Fertility returns rapidly after discontinuation, usually after 3–4 weeks from removal [42,54]. A non-contraceptive benefit of the ETN subdermal implant is a significant decrease in dysmenorrhea [55].

After ETN subdermal implant insertion, changes in menstrual bleeding patterns are common and include amenorrhea or infrequent, frequent, or prolonged bleeding [42].

In the event of cycles with luteal activity, there is a consistent percentage of luteinized unruptured follicles among implant users [56].

Complications related to its insertion (1%), such as pain, slight bleeding, hematoma formation, deep or incorrect insertion, unrecognized non-insertion, and removal (1.7%) are uncommon. All healthcare providers who perform implant insertions and removals must receive training. Other complications include gastrointestinal disorders, cephalea, mastodynia, and acne (10–14%) [42].

The limited evidence available is reassuring regarding bone mineral density, a surrogate marker for fracture risk [57].

In the long term, the ETN subdermal implant does not appear to be associated with an increased risk of thrombotic stroke and myocardial infarction [58], but according to WHO medical eligibility criteria, it is contraindicated in women with acute deep VTE, a personal history of severe liver disease, or breast cancer [59].

No daily-hormonal contraception in specific settings

It is relevant to underline that no-daily contraceptives can be attractive alternatives to COC, especially in unique and specific settings where the personalization of the contraceptive method is essential. This benefit is critical for example in adolescents, perimenopausal patients, obese women, patients with intestinal malabsorption or eating disorders, breastfeeding women, and post-voluntary termination of pregnancy (Table 4).

Adolescents

In the absence of medical contraindications, all currently available contraceptives are safe and effective for use in adolescents [60]. Non-contraceptive side effects of hormonal contraception, such as improvement in acne, hirsutism, and dysmenorrhea may also play a key role in the decision-making process [61].

Regarding skin patches, adolescents cite cost concerns, skin irritation, and detachment or loosening of the adhesive patch as the most common reasons for discontinuation [62]. For adolescents, comfort using a vaginal product such as tampons, as well as positive feelings and knowledge of reproductive anatomy, is associated with an increased willingness to try a contraceptive vaginal ring [63].

Since adolescents and young women (less than 21 years old) who use SARC have significantly higher contraceptive failure rates than older women [64], LARC appears to be a viable alternative in this category of patients since they require no action on the part of the adolescent after placement, resulting in typical use rates that closely approximate perfect use [65]. Both the American College of Obstetrics and Gynecology (ACOG) and the American Academy of Pediatrics (AAP) recommend LARC use for adolescents, to decrease the rates of unintended adolescent pregnancy and abortion [66]. Adolescents are often nulliparous, evidence suggests that

Table 4. Recommendations and use of no-daily contraception in specific settings LARC: long-acting reversible contraceptives; LNG-IUD: levonorgestrel-releasing intrauterine system; ETN etonogestrel; EE: ethinylestradiol; IUC: Intrauterine contraception.

Recommendations and use of no-daily hormonal contraception in specific settings	
Adolescents	• *LARC* use is recommended to decrease the rates of unintended pregnancy and abortion → they require no action after placement.
Perimenopause	• Above 40 years of age, careful assessment of cardiovascular, metabolic, medical history and lifestyle risks is essential. • The *LNG-IUD* with additional estrogen and vaginal ring is effective for perimenopausal symptoms.
Obesity	• *LNG-IUD* safe and effective contraceptive method for obese women without contraindications. • *LNG-IUD* is not associated with an increased risk of VTE and exerts only minimal effects on plasma lipids and glucose metabolism. • *ETN subdermal implant* has a nonrelevant impact on fasting glucose and insulin in obese women. • Earlier replacement of the *ETN subdermal implant* after 24 months may be considered.
Eating disorders or intestinal malabsorption	• No-daily contraceptive methods avoid the oral route.
Breastfeeding	• *Progestin-only* contraceptives do not adversely affect a woman's ability to initiate and continue breastfeeding or an infant's growth and development. • *ETN subdermal implant* and *LNG-IUD* can be used 6 weeks after delivery.

Post-voluntary interruption of pregnancy	• *LARC*: a good option for women who have a higher risk of forgetfulness or repeated voluntary interruption of pregnancy.
	  ◦ *IUC and the ETN subdermal implant* can be inserted concurrently with surgery or at the time of the follow-up visit.
	• For medical abortion:
	  ◦ *IUC* can be inserted from the time that abortion has been established.
	  ◦ *ETN subdermal implant* can be inserted at the time of mifepristone administration.
	  ◦ *Contraceptive patch, contraceptive ring, and ETN subdermal implant* should be given immediately after the first pill of the medical abortion regimen.

complications such as uterine perforation, ectopic pregnancy, and pelvic inflammatory disease are uncommon in all users, including adolescents and nulliparous women [42]. Analysis of CHOICE study data suggest expulsion rates may be higher in adolescents than in older women, and lower in nulliparous than in parous women. A Cochrane review [67] showed that naproxen 300 mg in two separate doses may decrease pain in the first hours after insertion in nulliparous women. Lidocaine 4% topical gel may lessen pain during IUC insertion and shortly thereafter in nulliparous women, while lidocaine and prilocaine cream, and 1% paracervical block may be effective but they have not been specifically studied for nulliparous women. The wait time between application and intervention for these medications to act ranges from three to seven minutes.

Perimenopause

No method is contraindicated based on age only; however, above 40 years of age, COC is considered MEC category 2 [43], underlining the need for special prescriptive care in this category of patients. In this age group, careful assessment of cardiovascular, metabolic, medical history and lifestyle risks is mandatory. Although in most of these patients, low-dose estrogen can be used.

Contraception with progestin alone may be a viable alternative in smokers and in those individuals having high BMI, diabetes associated with vascular complications, or in the presence of migraine. However, progestin-only contraception poorly controls vasomotor symptoms.

In perimenopausal women with no contraindications, the LNG-IUD with additional estrogen when indicated appears effective for perimenopausal symptoms and long-term benefits associated with the contraceptive effect [4, 68]. Vaginal ring can also be a good option for nonsmoking perimenopausal women [69].

Obesity

In obese women, the baseline risk for VTE is a 2–4-fold increase in comparison to normal-weight women, and it increases with age [51]. A Cochrane Review concluded that there is no general evidence of an association between BMI and decreased efficacy with combined hormonal contraception (CHC) [70], but CHC further increases the risk for VTE in obese women. Therefore, these contraceptive methods should only be used if no other acceptable contraceptives are available or acceptable, or if the benefits still outweigh the risks [71].

It appears that in women using the transdermal patch, a weight of > 90 kg appears to be associated with an increased rate of pregnancy [34,71].

There are currently little data on the efficacy of the contraceptive vaginal ring in obese women. In a prospective study on 20 normal weight (BMI 19–24.9) and 20 obese women (BMI 30–39.9) using EE and ETN contraceptive vaginal ring, it appears that contraceptive vaginal ring effectiveness is similar in women with a BMI up to 39.9. The lower serum EE levels in obese women may explain the greater reported bleeding or spotting days [72].

For the ETN subdermal implant, pregnancy rates are similarly low in obese, overweight, and normal-weight [73], though ETN plasma levels in obese women are lower [51]. Thus, even if epidemiologic and clinical data at present do not indicate a decreased efficacy in obese women caution is recommended. As ETN plasma levels decline over time an earlier replacement of the ETN subdermal implant after 24 months may be considered in women with BMI greater than 30 [51]. The ETN subdermal implant has a little and clinically nonrelevant impact on fasting glucose and insulin in obese women [74].

The LNG-IUD is a safe and effective contraceptive method for obese women without contraindications. With the LNG-IUD, LNG plasma levels are lower in obese women in comparison to non-obese, but because of the local effects of this system in the uterine cavity, efficacy should not be compromised. The system is not associated with an increased risk of VTE and exerts only minimal effects on plasma lipids and glucose metabolism. An advantage might also be the strong protection of the endometrium in these women [51].

Eating disorders

No-daily hormonal contraceptive methods avoid the oral route, this being very useful in case of eating disorders, where vomiting and diarrhea may cause the failure of COC [75].

Patients with a history of an eating disorder may have little subcutaneous tissue, which could theoretically increase the risk of deep ETN subdermal implant insertion [76]. Moreover, the

implant may be slightly more visible if patients have very thin arms [76].

Intestinal malabsorption

Since no-daily hormonal contraceptive methods avoid the oral route, they can be safely used in case of intestinal malabsorption. Gastrointestinal disorders, such as chronic diarrhea, gastroenteritis, inflammatory bowel disease, and celiac disease, speed up transit or alter absorption (ileostomy or jejunal bypass) and may cause the failure of COC [75]. Also, women who had bariatric surgery should be advised that the effectiveness of COC could be reduced [34], due to the risk of malabsorption [77].

Breastfeeding

For nursing mothers, more than 6 weeks after delivery [43] and postpartum nonbreastfeeding women more than 21 days postpartum, LARC contraceptive methods are categorized as MEC category 1, whereas CHC falls into MEC category 3 or 2 [43,40].

ETN subdermal implant does not interfere with breastfeeding and can be inserted immediately after delivery [43].

Risks for IUC-related events including expulsion, pain, infection, and removals appear similar or lower for breastfeeding women compared with non-breastfeeding women. Uterine perforation is rare; the risk appears 6- to 10-fold higher among breastfeeding compared with non-breastfeeding women [78]. In a prospective cohort study, the significantly increased risk of perforation among breastfeeding women was shown when IUC insertion occurred within 36 weeks (9 months) postpartum but not thereafter [41].

After-voluntary termination of pregnancy

Women who have experienced a voluntary termination of pregnancy are at high risk of repeating unintended pregnancies. Ovulation may resume as early as 10 days after the abortion [79]. LARC is a good option for adolescents, and women who have a higher risk of forgetfulness or in cases of repeated voluntary termination of pregnancy, to reduce the risk of error and failure [65, 80].

The IUC and the ETN subdermal implant can be inserted concurrently with the surgical procedure or at the time of the follow-up visit. For individuals undergoing medical abortion with the combination of mifepristone and misoprostol regimen or the misoprostol-only regimen, IUC can be inserted following complete abortion has been established [81]. Women who choose to have an IUC insertion immediately after abortion have higher rates of use compared with those who choose to insert the IUD after a time interval from the voluntary termination of pregnancy [82], and lower rates of repeated abortion than those who choose a non-IUC contraceptive method [83].

The ETN subdermal implant can be inserted at the time of mifepristone administration since ETN released from the ETN subdermal implant does not interfere with the action of mifepristone [81, 84]. Unintended pregnancy within six months after abortion appear lower with immediate insertion of the subdermal implant compared with delayed insertion (RR 0.25, 95% CI 0.08 to 0.77). There may be no difference between immediate and delayed insertion on rates of abnormal bleeding at one month after abortion [85].

The option of starting hormonal contraception should be given immediately after the first pill of the medical abortion regimen for individuals undergoing medical abortion who desire hormonal contraception, including contraceptive patch, contraceptive ring, and ETN subdermal implant [81].

Conclusions

In conclusion, no-daily hormonal contraception is a viable non-oral option for a wide range of women, due to its high effectiveness and many different extra-contraceptive benefits. These benefits are relevant to any woman desiring contraception. In addition, several subsets of patients may use no-daily contraception in different stages of their lives, with the possibility of choosing both LARC and SARC. Specific settings for its use are adolescence, perimenopause, obese women, eating disorders or intestinal malabsorption, breastfeeding, and post-voluntary termination of pregnancy. Furthermore, no-daily hormonal contraception limits or avoids the risk of forgetfulness. Each woman should be offered a method depending on her personal history and reproductive life phase using tailored contraceptive counseling based on the biopsychosocial model.

Further research perspectives in this area could address the acceptance of no daily SARC and LARC, especially in the young and adolescent population in regions where these methods have been introduced with more difficulty and delay, such as in southern Europe, and the reasons for this. It might be of interest to evaluate the most effective methods to reduce the main side effects of these contraceptive methods, such as spotting in subdermal implant carriers. In addition, the prevention of bone damage in individuals with eating disorders is a major issue that needs further investigation.

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