A revolution in contraception: new vaginal ring with progesterone and with segesterone acetate/ethinylestradiol, and combined oral contraception with estetrol

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ABSTRACT

Contraception is an essential component of birth control. The purpose of contraception is to prevent fertilization or implantation of a fertilized egg. Perfect contraception should be safe, effective, reversible, easy to use, widely available, and available at low/reasonable price. The choice of contra-ceptive method depends on many factors, the most important being the patient's wishes and acceptance. In the case of women with severe or chronic illnesses, or at high risk of adverse events, contraception should be carefully considered and the most appropriate method should be selected. Hormonal contraception is the use of progestogens only or progestogens in combination with estrogens.

The mechanism of the contraceptive effect of hormonal agents is complex, and it comprises the effect of preparations on the process of ovarian follicle maturation and ovulation, and their impact on the uterine mucosa, cervical mucus, and possibly on the contractility of the fallopian tubes.

Combined hormonal preparations vary greatly, both in their routes of administration and in their administration schedules. Oral contraceptive pills differ primarily in the type of progestogen used and in the ethinylestradiol dose.

A new vaginal ring with progesterone was developed for post-partum contraception. Segesterone acetate in combination with ethinylestradiol is becoming available in some parts of the world. Other novel options include combined oral contraception with estetrol and drospirenone.

In the following review, the advantages and disadvantages of the above methods of contraception are presented in order to familiarize readers with the latest methods of birth control.

KEYWORDS

Contraception, vaginal ring with progesterone, segesterone acetate/ethinylestradiol, combined oral contraception with estetrol.

Introduction

Choosing a method of contraception is a complex decision that should be made between the woman and the attending physician, often a gynecologist. Contraceptive counseling should provide the patient with the necessary factual information and help her to make the most appropriate decision regarding the choice of optimal contraception. We have many methods of contraception at our disposal, both hormonal and non-hormonal, among which condoms and birth control pills are still widely used. The choice of contraception method can be extremely difficult, because a series of factors need to be taken into account: cost, effectiveness, safety, availability, side effects, and reproductive plans [1].

Depending on their hormone content, contraceptives can be divided into non-hormonal contraceptives, hormonal contraceptives with progestogens, and hormonal contraceptives with estrogens and progestogens.

Among the non-hormonal contraceptives, the main methods are condoms and intrauterine devices with copper. Non-hormonal contraceptives do not affect the ovulation process, and therefore they do not influence the menstrual cycle. The presence of a non-hormonal intrauterine device (IUD) in the uterine cavity creates a local inflammatory reaction that appears to prevent sperm from reaching the fallopian tubes. Compared with hormonal preparations, the great advantage of non-hormonal contraceptives is that they do not cause the side effects associated with the use of hormones. Additionally, condoms, for example, protect against sexually transmitted diseases. However, IUDs with copper can, in many cases, intensify menstrual bleeding and pain [2].

Among the hormonal contraceptives with different types

Article history
Received 20 Nov 2021 - Accepted 24 Jan 2022

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of progestogen, the following options should be mentioned: hormonal IUD, 3-year subcutaneous contraceptive implant, 3-month contraceptive injection, single-component contraceptive pills with progestogens (used daily or post-coitally). The specific type of progestogen contained in these forms of contraception inhibits ovulation and endometrial receptivity, prevents sperm from entering the uterine cavity, and inhibits the growth processes in the uterine mucosa, which prevents implantation of the embryo.

A novelty among hormonal contraceptives containing different types of progestogen is a new vaginal ring with progesterone. It is intended for breastfeeding women up to 12 months after giving birth [3].

Among the known hormonal contraceptives containing estrogens and progestogens, we can list a vaginal ring, contraceptive patches, and contraceptive pills used in various regimens. Apart from inhibiting ovulation and endometrial receptivity, preventing sperm from entering the uterine cavity, the undoubted advantage of using combined contraceptives is the ability to better control menstrual bleeding. Among the estrogens, in the vast majority of cases, those used

so far are ethinylestradiol (EE), estradiol (E2) valerate, and 17 beta-estradiol. The only progestogens used in combined hormonal contraception are medroxyprogesterone acetate, drospirenone (DRSP), nomegestrol, dienogest, norgestrel, levonorgestrel, desogestrel, gestodene, norgestimate, norethisterone, and chlormadinone [4].

When it comes to hormonal contraceptives containing estrogens and progestogens, a novelty promoted in many countries around the world is a vaginal ring with segesterone acetate and EE.

In terms of combined oral contraception, a new drug that has appeared on the market is a pill containing estetrol (E4) in combination with DRSP.

Contraceptive vaginal rings

Vaginal ring with progesterone

More than 40 years ago, the evolution of contraceptive vaginal rings began, based on the fact that the vaginal epithelium can absorb steroid hormones. The main advantages of contraceptive vaginal rings are their effectiveness, ease of use, user control, nearly constant release rate allowing for lower doses of hormones, greater bioavailability, and good cycle control compared with oral contraceptives.

The first clinical trial of vaginal rings was published in 1970 by Dr. Dan Mischell [5]. A few rings contain of EE and E2 [6].

A trial of a progesterone vaginal ring was conducted in Santiago, Chile in the 1980s.

This progesterone vaginal ring has a diameter of 56 mm and measures 9 mm in cross-section. It is comprised of a silicon elastomer in which progesterone, 2 g, is homogenously dispersed. It is reserved for women from 4 weeks up to 1 year postpartum who breastfeed at least 4 times per day. It delivers 10 mg per day of hormone over 3 months. The progesterone vaginal ring inhibits ovulation and endometrial receptivity.

The progesterone vaginal ring is used to extend the contraceptive effect in breastfeeding women. Safety and efficacy trials have been carried out in Latin America where it is approved and currently in use in nine countries. The device is manufactured in Chile under the trade name "Progering®" [7]. It can be continued for over one year if breastfeeding is continued and a contraceptive effect is needed. The progesterone ring can be removed for 2 hours during intercourse but if the break is longer than this time, an additional contraceptive method should be applied for the next 7 days [7].

Clinical research had shown it to have high contraceptive efficacy (over 98.5%) and a good safety profile. The side effects include: urinary discomfort, bleeding disturbances, vaginal infections, and reproductive tract infections. The effectiveness of the progesterone vaginal ring is comparable to that of the Copper-T380A IUD. It is less effective than rings with estrogen and progestogen, but is reserved mainly for women in the puerperium. Studies in Australia, Canada, Chile, the United States, and Europe confirm that women accept the vaginal ring because of its effectiveness and ease of use (easy insertion and removal) [8].

Carr *et al*., in 2015, published a paper concerning safety of the progesterone-releasing vaginal ring in women during lactation. The researchers searched the PubMed, Popline, and LILACS bibliographic databases for articles, which were published in any language from database inception through October 1, 2014. The authors reviewed the literature for evidence regarding the safety of the progesterone-releasing vaginal ring among breastfeeding women and among their infants. All studies clearly revealed that use of the progesterone-releasing vaginal ring among lactating women compares favorably to other methods of contraception with regard to effectiveness. This method of contraception does not negatively affect breastfeeding and growth of babies in the first year after birth [9].

Another study performed by Roy *et al*., and published in *Contraception* in 2020, assessed and compared contraceptive efficacy, safety, continuation rates and duration of lactational amenorrhea in married lactating women using the progesterone vaginal ring or Copper-T380A IUD in the first postpartum year. The researchers conducted a one-year multicenter, non-randomized, non-inferiority, open-label, comparative study at 20 centers in India. Similar adverse events (progesterone vaginal ring: 24.2%; IUD: 23.0%) were reported in both groups. In women using the progesterone vaginal ring, no serious adverse effects were observed. Moreover, feeding and growth in newborn babies from both groups were comparable and basically as expected. The efficacy and safety results did not differ significantly between the two groups.

The progesterone vaginal ring continuation rates were shorter than the IUD rates, while women using the progesterone vaginal ring showed much longer-lasting amenorrhea during lactation than those using the IUD. Breastfeeding and infant growth/well-being patterns were favorable in both groups. The progesterone vaginal ring, a user-controlled device, offers an additional option of contraception to women during lactation for one year postpartum. This method of contraception can help address the unmet need for contraception among postpartum women while encouraging breastfeeding to increase the growth and well-being of babies [10].

Vaginal ring releasing segesterone acetate and ethinylestradiol

Segesterone acetate (16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-dione), is a 19-nor-pregnane derivative with no CH3 group radical in position 6 [11]. It was approved by the Food and Drug Administration (FDA) on August 10, 2018. It has a high binding affinity to progesterone receptors but shows negligible binding to androgen and estrogen receptors.

This new progestin, is suitable as a contraceptive agent, but also as a component of hormonal replacement therapy [12]. Segesterone acetate is rapidly inactivated if administered orally; instead, it is active not only transvaginally, but can also be used in implants and transdermal preparations [13].

When its relative binding affinities to human steroid receptors were investigated *in vitro*, segesterone acetate was shown to bind to the glucocorticoid receptor. However, it did not exert any glucocorticoid or mineralocorticoid activity in the *in vivo* assays, showing no increase in liver glycogen and tyrosine transaminase [14].

Segesterone acetate has no androgenic or estrogenic action *in vitro* or *in vivo*, and has no negative effect on the lipid profile. It has the highest anti-ovulatory potential of all available progestogens. A contraceptive vaginal ring releasing segesterone acetate and EE was found to be 97.5% effective in preventing pregnancy with a Pearl Index (PI) of 2.98 in the USA [15].

A contraceptive vaginal ring releasing 150 ug of segesterone acetate daily and 13 ug of EE [16] is used cyclically to provide 12 months (13 cycles) of contraception. This contraceptive vaginal ring is inserted into the upper two-thirds of the vagina and left in place for 21 days, then removed for 7 days. This once-a-month, self-applied device offers convenient, rapidly reversible, year-long contraception with efficacy and side effect profiles similar to those of other combined hormonal methods, for women with BMI < 29 kg/m^2. The segesterone acetate vaginal ring has a diameter of 56 mm and provides well control of menstrual bleeding. The adverse effects in women using the ring were similar in nature and frequency to those reported during the use of other hormonal contraceptives. Numerous studies have demonstrated the efficacy, safety and reversibility of segesterone acetate [17,18].

Huang *et al*. investigated effect of a one-year reusable contraceptive vaginal ring with nestorone, which is the old name for segesterone, and EE on the microflora of the vagina [19]. 120 women were enrolled into this study for over one year. The main complaint was vulvovaginal candidiasis, reported in 15%. Other side effects were bacterial vaginosis and dryness of the vagina. Segesterone acetate has been tested in subdermal implant form.

Vieira *et al*. [20] studied bleeding patterns among users of segesterone acetate (SA) and ethinylestradiol (EE) contraceptive vaginal system. Participants using the SA/EE contraceptive vaginal system up to 13 cycles reported good cycle control. Discontinuation due to unacceptable bleeding was very low.

In 2019, Gemzell-Danielsson *et al*. published a very important study on a safety assessment of the 12-month segesterone acetate/EE vaginal contraceptive system. The researchers evaluated clinical safety data from nine studies in which women used the contraceptive vaginal system for 21 consecutive days and removed it for 7 days of each 28-day cycle. They assessed safety by evaluating the adverse events the women reported in a daily diary and considered data from endometrial biopsies, vaginal microbiology, and liver proteins. The combined studies included 3052 women who received the vaginal contraceptive system. Women using the system most commonly reported the following adverse events: headache (*n*=601, 26%), nausea (*n*=420, 18%), vaginal discharge/vulvovaginal mycotic infection (*n*=242, 10%), and abdominal pain (*n*=225, 10%). Four (0.2%) women experienced venous thromboembolism, three of whom had risk factors for thrombosis like factor V Leiden mutation or BMI>29 kg/m^2. The 1-year segesterone acetate/EE vaginal contraceptive system has an acceptable safety profile, although additional studies are warranted in obese women at higher risk of venous thromboembolism. Its safety profile is similar to that of other combination hormonal contraceptives. The same precautions currently used for combination hormonal contraceptive prescriptions apply to this new vaginal contraceptive system [21].

In a 2020 review summarizing the segesterone acetate/EE vaginal ring as a novel method of contraception, Micks and Jensen reported that the bleeding pattern was highly favorable and consistent over the entire year and was associated with very low discontinuation. Efficacy and safety were similar to those of other methods of combined hormonal contraception. Unscheduled ring removals increase the risk of failure [22].

Segesterone acetate is also used for male contraception. 99 healthy males aged 18-50 years were enrolled to use transdermal gel with segesterone acetate and testosterone. The gel was applied for 24 weeks. Effective suppression of gonadotropin and spermatogenesis was observed in all the men; sperm concentration was suppressed to 1 million/mL or less in 88.5% of them. There were no significant adverse side effects [23].

Estetrol

Estetrol (E4) was discovered by Egon Diczfalusy *et al*. at the Karolinska Institute in Stockholm, Sweden in 1965 [24]. It is a naturally occurring estrogen which is produced only by human fetal liver in cooperation with the fetoplacental unit. It is synthetized from estradiol (E2) and estriol (E3) through the action of two enzymes: 15 alpha- and 16 alpha-hydroxylase. E4 is a steroid with 4-OH groups. Biochemically, it is closely related to estriol. Like estriol, it is classified as weak estrogen [25].

After its identification it was studied as a possible marker of fetal well-being, but with negative results. Later studies on the role of this hormone were suspended, but in recent years it has enjoyed a renaissance, as a natural estrogen that might be used in different hormonal therapies [26].

Estetrol presents moderate affinity for estrogen receptor alpha (ERα) and a lower affinity for ERβ. Its affinity for ERα is 5 times higher than for ERβ. Estetrol, in contrast to estradiol, does not bind to the estrogen membrane receptor. E4 has approximately 6% affinity for ER compared to E2. It is characterized by long half-life lasting 20-28 hours [27]. At the level of vagina, uterus and bone, estetrol presents estrogenic action.

Additionally, E4 is only metabolized to E4 glucuronate and sulfate, mostly excreted in urine, and not converted to other metabolites (as estradiol is).

Combined oral contraceptives with estetrol (E4)

The history of modern oral contraception started in the 1960s. Later, combined oral contraceptives (COCs) underwent an evolution. The idea was to prepare "ideal" oral contraceptives (OCs), able to ensure maximal safety and maximal efficacy. Ethinylestradiol is the oldest and most typical estrogen used in COCs [28]. However, it shows a negative impact on liver function and increases the risk of venous thromboembolism. Therefore, in the last decade the quantity of EE is COCs has been decreased. In 2009, E2 as an estrogenic component was included in COCs. Additionally, to obtain optimal COC parameters, modulation of different progestogen was used. However, the "ideal" estrogenic component of COCs is still waiting to be found/developed. Possibly E4 can be viewed as a candidate.

Studies conducted *in vivo* revealed that E4 has ability to inhibit ovulation in a dose-dependent manner [29]. The results of this study supported the idea of developing an E4-containing COC. The anti-ovulatory efficacy of different dosages of E4 in combination with two progestogens (levonorgestrel and DRSP) was analyzed in a phase II study in 2015 [30]. The highest ovulation suppression was observed in the 20 mg E4 group and was very similar to that observed with EE/DRSP. The minimal dosage able to suppress ovulation was above 10 mg of E4. The effects on endometrial thickness were comparable in all treatment groups.

The preparation with E4 had a similar effect on endometrial growth to that of EE/DRSP. Restoration of ovulation occurred rapidly, within 17-21 days of the last active treatment in all subjects. An important question needing to be answered was that of the impact of COCs containing E4 on bleeding pattern. Apter *et al*. [31] studied bleeding pattern and cycle control with an E4-containing OC (phase II study). The study involved 316 women. The authors found that 15mg of E4 combined with 3 mg of DRSP presented the most favorable bleeding pattern and cycle control. A year later, the same group published a study in which they found that 15 mg E4 together with 3 mg DRSP presents the best user-reported satisfaction in terms of bleeding control and body weight [32].

One of the most important aspects of COC use is, of course, its safety, which is mainly considered in terms of hemostatic and metabolic effects of COCs.

Some studies with E4 as a component of OCs evaluated the influence of E4 on liver function, lipid metabolism, bone markers and growth endocrine parameters. Mawet *et al*. [30] found a limited effect of E4 on the listed parameters [33].

Kluft *et al*. [34] analyzed the effects of E4 on plasma levels of sex hormone-binding globulin (SHBG), angiotensinogen, and 12 hemostasis markers. Both E4 combinations (5 or 10 mg E4 with 3 mg DRSP) showed low estrogen impact compared to EE/DRSP. Additionally, 10 mg E4 combined with DRSP had effects on angiotensinogen and SHBG that were 15–20% those of EE/DRSP. Both E4/DRSP combinations decreased D-dimer levels. The authors suggested that women who take E4-containing COCs may ultimately prove to have lower risk of venous thromboembolism compared with women who take EE-containing COCs.

Douxfils *et al*. [35] evaluated the impact of new combined COCs containing E4 on hemostasis parameters. These scientists reported that COCs containing 15 mg E4/3 mg DRSP present similar or decreased effect to those containing EE/LNG or EE/DRSP. This study also confirmed that the choice of estrogen modulates the effects of COCs on hemostasis parameters.

The Klipping *et al*. [36] study assessed the influence of the new OC formula E4/DRSP on endocrine and metabolic parameters, and revealed that the impact of this preparation on metabolic and endocrine aspects is limited. Preparations containing EE exert a more pronounced effect on gonadotropins, cortisol, corticosteroid-binding globulin (CBG), angiotensinogen, SHBG, and triglycerides.

Interesting findings concern the possible impact of E4 on breast cancers. According to contemporary knowledge estrogens exert a negative influence on mammary tissue by increasing mitogenic activity. Gérard et al. found that E4 presents anti-tumor activity by decreasing the strong proliferative effect of E2 and has a limited impact on breast cancer [37].

A recent (2021) study by Gemzell-Danielsson *et al*. [38] assessed the contraceptive efficacy, bleeding pattern and safety of a COC containing E4 15 mg and DRSP 3 mg. A large, multicenter, open-label and phase 3 trial was performed in 69 sites in Europe and Russia. A group of 1553 women aged 18-50 years participated in the study. The PI was 0.47 pregnancies/100 woman-years. The percentage of abnormal bleeding/spotting in the women studied decreased from 23.5% in cycle 1 to <16% from cycle 6 onwards. Given the frequency of side effects, the study dealt with headache (7.7%), metrorrhagia (5.5%), vaginal hemorrhage (4.8%) and acne (4.2%). One serious side effect observed, namely a lower extremity venous thromboembolism. The conclusions were that a COC containing E415 mg and DRSP 3 mg seems to be an effective and safe method of contraception [38].

In a very important study by Creinin *et al*. [39], published in *Contraception* in 2021, the researchers, as above, assessed the efficacy, cycle control, and safety of an oral contraceptive containing E4 15 mg and DRSP 3 mg. 1864 women aged 16-50 years with a body mass index ≤35 kg/m^2 were enrolled in the study, which was also a multicenter, open-label, phase 3 trial. Women between 16 and 35 years of age had a PI of 2.65 pregnancies/100 women-years.

Unscheduled bleeding decreased from 30.3% in cycle 1 to 21.3% to 22.1% during cycles 2 to 4. The most frequently reported adverse events were headache (5.0%) and metrorrhagia (4.6%). The conclusions of this study, similar to those of Gemzell-Danielsson *et al*., were that the described contraceptive method "is an effective oral contraceptive with a predictable bleeding pattern for most women and has low AE rates" [39]. Analysis of the presented data suggests that E4 can be viewed as a new, promising estrogenic component of COCs.

The great advantage of E4 is its high efficiency and safety related to the influence on the metabolic profile and the risk of thromboembolism.

Conclusions

In conclusion, as can be seen from the present review, none of the methods of contraception commonly used in the world

are ideal. Each of them is associated with various types of more or less troublesome side symptoms. Each of them is also characterized by positive aspects, which we should first of all take into account when choosing the right method of contraception.

The contraceptive method should be selected individually for each patient. Newly introduced types of contraception should be thoroughly researched and tested before being accepted and put on sale. Therefore, numerous studies are carried out, focusing on modification of known methods of contraception, and on the constant search for completely new methods of birth control. The construction of a modern method of contraception in the form of a ring with progesterone and another ring containing segesterone acetate combined with EE, as well as the new estrogen estetrol combined with drospirenone may all contribute to improvements of the effectiveness and safety of contraception.

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Acknowledgements: *No any financial support received.*
Conflict of interest statement: *The authors declare that there is no conflict of interest.*