EXPERT OPINION

Dienogest in the treatment of endometriosis

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Introduction: Dienogest (DNG) is an oral progestin, derivative of 19-nortestosterone, that has recently been introduced for the treatment of endometriosis.
Areas covered: This review examines the clinical efficacy, safety and tolerability of DNG in the treatment of endometriosis. The material included in the current manuscript was searched and obtained via Medline, Pubmed and EMBASE, from inception until February 2014. The term 'dienogest' was associated with the following search terms: 'endometriosis', 'pharmacokinetics', 'safety' and 'efficacy'.
Expert opinion: Several trials demonstrated the clinical efficacy, safety and tolerability of DNG. However the use of DNG is associated with some limitations. So far, no study investigated the potential of contraceptive effect of this treatment and therefore, it should be recommended with other methods of contraception (e.g., barrier methods). A further limitation of the use of DNG as daily therapy in the long term is that the cost of the therapy is higher than other progestins available on the market and combined oral contraceptives. Therefore, future studies should be designed to compare the efficacy and safety of DNG with other progestins.

Keywords: dienogest, efficacy, endometriosis, hormonal, pharmacokinetics, progestin, safety

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1. Introduction

Endometriosis is a chronic estrogen-dependent gynecological condition characterized by the presence of ectopic glands and stroma outside the uterine cavity. It affects at least 5 – 10% of women [1], and it often causes infertility and/or pain symptoms (dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia). In some patients, pain symptoms are extremely severe and negatively affect quality of life (QoL), work efficiency and sexual life [2-4]. The definitive diagnosis is only histological. The role of surgery is both diagnosis and treatment but often, especially in patients with less extensive disease, the first therapeutic approach is medical treatment based on the suspicion of the presence of endometriosis achieved through a gynecological examination, transvaginal ultrasound and eventually pelvic MRI [5,6].

Several hormonal therapies have been proposed for the treatment of endometriosis-related pain, including oral contraceptive pill and other estroprogestin formulations (such as the vaginal ring and the transdermal patch), progestins (including medroxyprogesterone acetate, norethisterone acetate, desogestrel and the levonorgestrel-releasing intrauterine device), gonadotrophin-releasing hormone (GnRH) agonists and hyperandrogenic compounds (such as danazol and gestrinone) [5]. These traditional endocrine therapies for endometriosis inhibit estrogens production in the ovary. However, medical therapy is a purely symptomatic treatment. In fact, the symptoms usually recur when discontinuing

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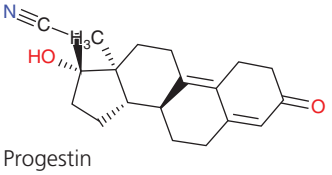
Box 1. Drug summary.

Drug name	Dienogest
Phase	Launched
Indication	Endometriosis
Chemical formula	17α-Hydroxy-3-oxo-19-norpregna-4, 9-diene-21-nitrile
Molecular formula	$C_{20}H_{25}NO_2$
Chemical structure [64]	
Pharmacology description	Progestin
Route of administration	Oral
Dosage	2 mg once daily

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the therapy. As patients with endometriosis require long-term therapies, it is important to choose the agents with the lowest effective dose and with minimal adverse effects.

GnRH agonists (such as leuprorelin acetate, buserelin acetate (BA) and triptorelin) are currently considered the most effective drugs in relieving pelvic pain associated with endometriosis [7], but they cause many adverse effects related to the hypoestrogenism (hot flushes, osteopenia, mood swings, vaginal dryness). These adverse effects may be buffered by associating GnRH agonist with 'add-back therapies' (e.g., tibolone or progestins). Hyperandrogenic compounds cause adverse androgen-like effects (such as acne, seborrhea, hirsutism, alopecia and weight gain); in addition, they may cause unfavorable changes in the levels of cholesterol in the blood (higher low density lipoprotein [LDL]-cholesterol and lower high density lipoprotein [HDL]-cholesterol) [8]. The combined oral estrogen-progestin pill (COCs) is currently one of the first choices among symptomatic medical therapies available for the treatment of endometriosis-associated pain. Among the available pills, it is preferable to choose those with a lower content of estrogen in order to decrease the endometrial stimulation [9]. Even if COCs are very frequently prescribed to alleviate pain symptoms in endometriosis, there is a lack of randomized controlled trials on the efficacy of this treatment and, nowadays, they are not approved for treatment of endometriosis-associated pelvic pain (EAPP) [10]. Among progestins, the most widely used are norethindrone acetate (NETA, 2.5 mg/day) and the levonorgestrel-medicated intrauterine device (Lng-IUD), which after insertion lasts for 5 years. As we said for COCs, similarly, Lng-IUD is not approved for the treatment of endometriosis. Other progestins are desogestrel, medroxyprogesterone acetate (oral or depot) and antiprogestogens (such as gestrinone). NETA allows the achievement of amenorrhea in about two-thirds of the cases [11], whereas the Lng-IUD causes amenorrhea in one-third of cases reducing bleeding in another third of cases [9]. Therefore, these progestins are particularly useful in patients suffering from mainly dysmenorrhea. Other progestins have been used in clinical practice to treat endometriosis (chlormadinone acetate, promegestone and nomegestrol acetate); however, their effectiveness is not supported by scientific studies. Progestins are frequently used as first-line therapy for the treatment of endometriosis. They exhibit an antigonadotropic effect, which inhibits ovarian function to create a hypoestrogenic environment. By directly acting on endometrial progesterone receptors, they induce decidualization of endometriotic lesion. Lastly, they have been shown to reduce peritoneal inflammation [12]. Progestins have shown results comparable to surgery in the treatment of dyspareunia associated with endometriosis [11], are effective in reducing pain in patients with intestinal endometriosis [13], are successful in eradicating symptoms and producing regression of recurrent endometriomas [14] and have proven effective in the treatment of rectovaginal endometriosis [15,16]. However, progestins have some adverse effects, including the acne, weight gain, headaches and irregular menstrual bleeding. Over the last few years, new therapies have been developed to target pathogenic molecular pathways involved in the process of endometriosis. Among these agents, there are aromatase inhibitors, antiangiogenic agents, selective estrogen receptor modulators, anti-inflammatory agents (such as COX2 inhibitors or pentoxifylline) and statins [17].

Dienogest (DNG) is a derivative of 19-nortestosterone that has recently been introduced for the treatment of endometriosis (**Box 1**). This review examines the clinical efficacy, safety and tolerability of DNG in the treatment of endometriosis. The material included in the current manuscript was searched and obtained via Medline, PubMed and EMBASE, from inception until February 2014. The term 'dienogest' was associated with the following search terms: 'endometriosis', 'pharmacokinetics', 'safety' and 'efficacy'. All pertinent manuscripts were carefully evaluated and their reference lists were examined in order to find other articles that could be included in the present manuscript.

2. Chemistry of DNG

DNG (17α-hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile) is a derivative of 19-nortestosterone [18], but it differs from other progestins of the same derivation for the presence of a cyanometilic group in place of an ethynyl group in position 17α. Thus, DNG combines the advantages of 19-nortestosterone derivatives (such as the short plasma half-life, the powerful progestin effect on the endometrium and high bioavailability) with the benefits of progesterone derivatives (such as antiandrogenic activity and a moderate inhibition of gonadotropin secretion) [19-21].

Table 1. Pharmacokinetic of dienogest [22,23,25].

Absorption	After oral administration of a film-coated tablet of 2 mg dienogest: Bioavailability: 90.5% AUC24 h: 441 ± 92 ng·h/ml; AUC∞: 535 ± 137 ng·h/ml; C_{max}: 47.6 ± 8.7 ng/ml; $T_{1/2}$: 9.4 ± 1.9 h; T_{max}: 1.5 h No influence of concomitant food intake Dose-dependent pharmacokinetics in the range of 1 – 8 mg
Distribution	Plasma binding: Albumin: 90% SHBG, CBG: 0% Free, unbound: 10% Distribution volume after a single dose of 1 mg: 40 L Steady state: 6 days No accumulation of the drug
Metabolism	Hydroxylation of double bonds, hydrogenation and aromatization reactions that makes the dienogest to inactive metabolites that are excreted quickly so DNG is the predominant fraction in plasma Main enzyme involved: CYP3A4 Metabolic sieric clearance (Cl/F): 64 ml/min
Excretion	Urine (free steroids 20 – 30%; 'glucuronide' fraction 25% and 'sulfate' fraction 22%) Decrease in serum in two phases Terminal half-life of distribution: approximately 9 – 10 h The proportion of metabolites excreted in the urine compared with the fecal is 3:1 after oral administration of 0.1 mg/kg Half-life of urinary excretion of metabolites: 14 h After oral administration, ~ 86% of the dose was excreted within 6 days, most within 24 h, primarily in the urine

DNG: Dienogest; SHBG: Sex hormone binding globulin.

3. Pharmacokinetic of DNG

When the DNG is administered orally at a dose of 2 mg, the bioavailability is high, amounting to ~90.5% (**Table 1**) [22]. The absorption of DNG is fast. By administering a 2 mg tablet DNG under fasting, the C_{max} is about 40.9 ± 11.0 ng/ml with an interval of about 1.75 h (T_{max}) between intake and maximum plasma peak. The half-life time ($T_{1/2}$) is 8.9 ± 1.7 h. The area under the plasma concentration time curve (AUC) from time zero to infinity (AUC∞) is about 453 ± 135 ng × h/ml and from time zero to 48 h it is about 438 ± 123 ng × h/ml [22].

Pharmacokinetic parameters after oral administration of a film-coated tablet of 2 mg DNG given as single dose and after 14 days of dosing are respectively as follows: AUC24 h 441 ± 92 and 547 ± 129 ng·h/ml; AUC∞ 535 ± 137 and 682 ± 205 ng × h/ml; C_{max} 47.6 ± 8.7 and 52.2 ± 8.3 ng/ml; $T_{1/2}$ 9.4 ± 1.9 and 10.2 ± 1.8 h; T_{max} 1.5 and 1.25 h [22]. In a study of female volunteers who received single oral doses of DNG in consecutive menstrual cycles, the mean peak of serum concentrations (C_{max}) were 28, 54, 101 and 212 ng/ml after 1, 2, 4 and 8 mg doses, respectively. The mean areas under the serum concentration curve (AUC∞) were 306, 577, 1153 and 2292 ng·h/ml, respectively [23].

The influence of food on absorption is small [22]. DNG is poorly absorbed through the skin as has been highlighted in a study after administration of 10 mg of DNG transdermally in healthy male volunteers [23].

Ninety percent of DNG binds unspecifically to albumin, whereas only 10% is present in plasma in the free form [21]. DNG does not bind to the sex hormone binding globulin (SHBG) or corticoid binding globulin; therefore, the administration of DNG does not alter the plasma levels of these proteins. As testosterone is not displaced from the protein that binds in plasma, DNG does not increase the levels of serum testosterone and it does not have androgenic effects [22].

The apparent distribution volume of DNG is about 40 l after single oral dose of 1 mg [23]. In repeated administrations of oral tablets of DNG 1 mg, steady state is reached within 6 days and there is no accumulation of the drug [23].

A recent review [24] compared the pharmacokinetic characteristics of DNG with other progestins derivatives of C 19-nortestosterone (such as norethisterone, levonorgestrel, 3-keto-desogestrel and gestodene). This comparison showed that DNG is the only progestin that does not bind SHBG, has no influence on the kinetics of testosterone and has no androgenic effects. Moreover, DNG has the highest free-unbounded fraction in the plasma (about 10%). The high circulating levels of free DNG explain the wide penetration of the molecule in different tissues.

The metabolic pathway of DNG is mainly composed of hydroxylation of double bonds, but also hydrogenation and

aromatization reactions, which transforms DNG in at least nine inactive metabolites [22,23]. The metabolites have lower affinity to progesterone receptor compared with DNG [23]. CYP 3A4 is the most widely used enzyme in the metabolic pathway of DNG [25]. The excretion of DNG takes place mainly through the urine after glicuronide and sulfate conjugation and most of the metabolites are eliminated in the first 24 h. As the metabolites are not hormonally active and are excreted very rapidly, DNG is the predominant fraction in plasma. A fraction of ~20 – 30% of the total excreted in the urine is released as free steroid [22]. The serum clearance of DNG is ~ 64 ml/min [22]. The half-life for excretion of urinary metabolites is ~ 14 h [22].

As DNG is metabolized primarily by CYP3A4, coadministration of drugs inducers or inhibitors of this cytochrome alters the concentration at steady state, particularly when DNG is administered in association with estradiol valerate. Inducing drugs include rifampin, carbamazepine, phenobarbital and phenytoin, whereas erythromycin, ketoconazole, itraconazole, nefazodone, ciprofloxacin, fluvoxamine and grapefruit juice are CYP3A4 inhibitors.

DNG should not be administered to patients with hepatic insufficiency; therefore, acute or chronic diseases of the liver represent a contraindication to the administration of the drug [22]. Up to now, no study evaluated the pharmacokinetics of DNG in patients with renal insufficiency [25]. There is no difference in the pharmacokinetics of DNG in pre- and postmenopausal women [25].

4. Pharmacodynamic of DNG

Synthetic progestins can be divided according to their molecular structure and their functional characteristics into two categories: the derivatives of progesterone (such as medroxiprogesterone acetate and megestrol acetate) have a progestogenic and androgenic activity; the derivatives of 19-nortestosterone, which are not approved for the treatment of endometriosis, have strong activity on the endometrium, with mild androgenic, estrogen and glucocorticoid activity [26].

DNG has pronounced effects on the endometrium that is the basis of its efficacy in the treatment of endometriosis. Studies *in vitro* demonstrated that DNG has moderate affinity for progesterone receptors that is ~10% of the affinity of natural progesterone [23]. DNG has strong antiandrogenic activity, whereas it has no glucocorticoid and mineral corticoid effects. It also does not activate estrogen receptors, neither α type nor β type [20,27].

In vivo, DNG has important progestational effects; it inhibits gonadotropic release, but does not have glucocorticoids, mineral corticoids or significant estrogen-like effects [20,23,27]. Despite DNG having low affinity for progesterone receptors, it has a pronounced progestin effect *in vivo* that can be attributed to the high levels of plasma-free molecule [19]. Therefore, DNG combines the advantages from the pharmacodynamic point of view of the derivatives of 19-nortestosterone with those of progesterone.

The strong activity of DNG on endometrial tissue has been demonstrated by investigations in both humans (Kaufmann assay) [20] and rabbits (McPhail test) [21]. DNG shows strong activity on the endometrium when compared with its activity of inhibiting ovulation. This feature results in a high ratio between the dose inhibiting ovulation and the dose that leads to the transformation of the endometrium (uterotropic index), which appears to be the highest among all progestins [18,21,27].

When administered at the dose indicated for the treatment of endometriosis (2 mg/day), DNG reduces serum levels of progesterone to anovulatory levels. The action on the ovary is peripheral rather than central as the serum levels of gonadotropins (follicle-stimulating hormone and luteinizing hormone [LH]) do not undergo significant variations. Studies assessing the ultrasound characteristics of the ovaries of patients under treatment with DNG showed that follicles did not exceed the size of 10 mm maximum diameter [28]. A randomized trial [29] investigated the minimum dose of DNG inhibiting ovulation by randomizing 102 participants to receive 0.5, 1, 2 or 3 mg/day of DNG; estradiol and progesterone serum levels and the size of the follicles were evaluated every 3 days. The study showed that the lowest dose of DNG capable of inhibiting ovulation was 2 mg/day, both in short-term (1 – 36 days) and long-term (36 – 72 days) observation. Another study suggested the lowest dose able to inhibit ovulation of healthy women of fertile age between 20 and 39 years old is 0.6 mg/day when administered in a single dose during the follicular phase of the menstrual cycle [30]. The administration of 2 mg DNG 2 days before the expected time of ovulation prevents ovulation itself. Whereas when DNG is administered 1 day before ovulation (0.5 or 2 mg), ovulation occurs but the LH peak is lower without anyway alteration in the function of the corpus luteum. Furthermore, ovulation and the corpus luteum function are not altered by the administration of DNG (both 0.5 and 2 mg) during the peak of LH. The menstrual cycle does not undergo alterations when DNG is administered after the occurrence of ovulation. These results demonstrate that DNG in a single-dose administration in midcycle can alter pituitary and ovarian function depending on the time interval between administration and the day of LH-surge [30]. Moreover, the anovulatory action ceases when the drug is discontinued. At a dose of 2 mg/day, the plasma levels of E2 are not completely suppressed but remain comparable to those of the early follicular phase having an important implication from the clinical point of view, that is, the absence of the occurrence of secondary effects caused by hypoestrogenism (such as hot flushes and bone loss), where instead effects are observed during treatment of endometriosis with GnRH analogs [31].

When DNG is compared with other progestins (such as NETA, levonorgestrel, gestodene, desogestrel, norgestimate, cyproterone acetate, chlormadinone acetate), it shows more potent progestational effects on the endometrium and weaker

actions of suppression of gonadotropins release [24]. DNG causes an inhibition of ovulation 3.5 times greater than levonorgestrel in the rabbit and 7 times greater than levonorgestrel in the rat [18].

No study evaluated the contraceptive effectiveness of DNG; therefore, women using this drug are advised to use nonhormonal contraception (such as barrier methods) to prevent unwanted pregnancies. After cessation of therapy with DNG, normal ovarian activity and menstrual cycle recover quickly; there have been reports of women conceiving shortly after the end of treatment, including women with previous history of infertility [32].

Few studies investigated the influence of DNG on the breast. A small trial [33] evaluated the ultrasonographic changes induced on the mammary gland by the use of DNG at high dose (10 mg twice a day [b.i.d.] for 24 weeks), demonstrating a reduction of the size of the mammary gland and a reduction of the mastopathic lesions that were present before starting treatment. However, further studies are needed to evaluate the relationship between the use of DNG and breast cancer and to compare the effects of DNG on the breast with other progestogens.

The use of DNG (up to 20 mg/day for 24 weeks) does not cause clinical changes in thyroid function, hemostatic parameters, liver enzymes, metabolism of carbohydrates and lipids [34-36].

5. Mechanism of activity in endometriosis

DNG inhibits endometriotic lesions through different mechanisms. In rabbits, it exerts a moderate inhibition of the secretion of gonadotropins, which decreases the endogenous production of estradiol, thus limiting its trophic action on the eutopic and ectopic endometrium [20,21]. It creates a hyperprogestogenic and hypoestrogenic environment that initially induces a secretory state and then a decidualization of the ectopic endometrium and finally its atrophy if the treatment is not discontinued [22]. Other studies showed *in vitro* and *in vivo* on rats an inhibitory action of DNG on the proliferation of endometrial cells mediated by modulation of the expression of matrix metalloproteinases, which are involved in the regulation of ectopic endometrial response to estrogen [37]. Finally, other animal studies have hypothesized the inhibition of angiogenesis by the DNG as a further mechanism of action [38]. Because DNG inhibits aromatase and COX-2 expression as well as prostaglandin E2 production in endometriotic stromal cells in experimental *in vitro* study, these pharmacological features might contribute to the therapeutic effect of DNG on endometriosis, thus demonstrating the important anti-inflammatory effect of DNG that is relevant in reducing the size of the endometriotic lesions [39]. The average serum concentrations of E2 remain in the range of 20 – 50 pg/ml when DNG is administered at a dose of 2 mg/day, thus showing only moderate estrogen suppression [27]. Therefore, when DNG is administered at the dose of 2 mg, E2 levels remain within the 'therapeutic window' in order to avoid stimulating effects on the lesions and hypoestrogenic side effects, such as bone mineral density (BMD) loss [29,40].

One study [41] investigated the effects of DNG on experimental endometriosis. In rats, DNG (0.1, 0.3 or 1 mg/ kg) causes histological changes in endometriotic implants comparable to those observed after danazol administration, but DNG is less marked than GnRH analog or ovariectomy. All treatments induce a reduction in the volume of the endometriotic implants when compared with placebo. On the other hand, DNG has a lesser effect on BMD when compared with danazol, buserelin or ovariectomy. Moreover, it was shown that even the combination of DNG with buserelin had a lower impact on BMD compared with buserelin alone. Furthermore, the same study showed that DNG normalizes the activity of natural killer cells and decreases the release of interleukin-1β by macrophages [41].

Another recent study [42] demonstrated the potent inhibitory activity of ectopic endometrial tissue obtained by autotransplantation of uterine tissue into peritoneal cavity of rats. In these rats, DNG was administered at a dosage of 0.3 or 1 mg/kg/day for 28 days. At laparotomy, DNG demonstrated a significant reduction of the total endometrial lesion area, thus confirming the effectiveness of the compound in decreasing the size of endometrial lesions [42].

6. Clinical efficacy

Progestins have been used for many years as medical therapy of endometriosis, although there is limited evidence resulting from controlled studies (particularly those against placebo) that supports the effectiveness of many compounds in this class. DNG is the only oral progestin that has been specifically designed for the treatment of endometriosis and its efficacy has been investigated by several studies with a comprehensive design including randomized, dose-ranging [43], double-blind comparison with placebo [44], comparison versus GnRH agonists [31] and finally studies of efficacy and tolerance in long term [32].

DNG is effective in reducing endometriosis-related pain symptoms such as dysmenorrhea, premenstrual pelvic pain, dyspareunia and chronic pelvic pain. Its efficacy is superior to placebo and equivalent to GnRH agonists, but with a better tolerability profile. As pain relief is one of the main goals of therapy in patients with endometriosis, it should be considered an indicator of treatment success [44,45].

6.1 Dosage comparison

The optimal dose that guarantees the resolution of symptoms during treatment with DNG was assessed in a 24-week, randomized, open-label study including 68 women with endometriosis stages I, II and III accordingly to the revised American Fertility Society (rAFS) classification [43]. Women were randomized to receive DNG once daily at the doses of 1, 2 or

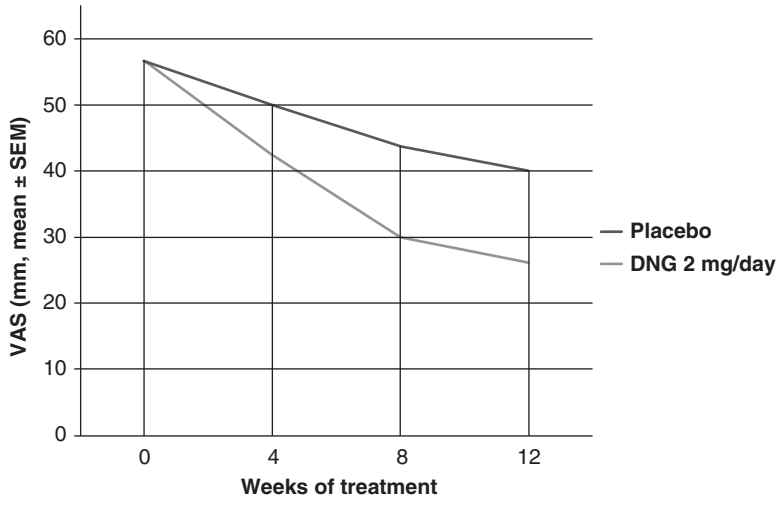

Figure 1. Superiority of DNG 2 mg/day versus placebo for 12 weeks ($p < 0.0001$).
Reproduced with permission from [44].
DNG: Dienogest; SEM: Standard error of the mean; VAS: Visual analog scale.

4 mg. Randomization in group with 1 mg was stopped due the unsatisfactory control of the cycle, with irregular menstrual bleeding. DNG at the dose of 2 and 4 mg daily caused improvement of symptoms in a large number of women. The prevalence of dyspareunia decreased from 51.7% (baseline) to 6.9% at 24 weeks in the 2 mg group and from 57.1 to 5.7% in the 4 mg. Similar results were also achieved for other symptoms such as diffuse pelvic pain. Regarding the pain reported by the woman during the clinical examination, this was reduced by 75.9% (baseline) to 44.8% in the 2 mg group and by 73.2% (baseline) to 21.4% in the group of 4 mg. Therefore, based on the results of this study, the dosage of 2 mg/day of DNG was chosen for the treatment of endometriosis.

Another study of dosage comparison was made by a Japanese group [46] that compared DNG administered at a dose of 1, 2 and 4 mg/day for 24 weeks divided into two daily doses. The study included 187 patients. The study concluded that there was an improvement in symptoms with the three different dosages but the comparison between these dosages was not statistically significant. Instead, there was a statistically significant difference ($p < 0.001$) in the comparison of dosage as regards the level of plasmatic E2. Mean serum estradiol concentrations at between 8 weeks and the end of treatment in this study were 84.5, 37.4 and 26.2 pg/ml for DNG doses of 1, 2 and 4 mg/day, respectively. On the basis of the reduction in plasma E2, the 2 mg/day dose was considered to be the optimal dosage in Japan. A serum estradiol concentration in the range of 30 – 50 pg/ml is considered sufficient to inhibit endometriotic lesion growth and it is adequate to prevent hypoestrogenic side effects such as bone mineral loss [47].

6.2 Double-blind comparison with placebo

DNG (2 mg/day) was compared with placebo in a 12-week, randomized, double-blind study including 188 premenopausal women with endometriosis [44]. The patients had laparoscopically confirmed endometriosis (stages I–IV according to the classification rASRM), with laparoscopy performed within 12 months before the study and baseline EAPP score > 30 mm on the visual analog scale (VAS). Approximately 70% of the patients included in the study had endometriosis at stages III–IV. The average VAS scores decreased by 27.4 mm in the DNG group and 15.1 mm in the placebo group during the 12 weeks of the study, resulting in a difference between the two groups of 12.3 mm, which was statistically significant in favor of DNG (IC 95%: 6.4 – 18.1, $p < 0.0001$) (**Figure 1**). A secondary efficacy end point in the placebo-controlled study was the score Biberoglu and Behrman (B & B). This score confirmed the results of the primary end point, demonstrating a greater reduction in signs and symptoms in the DNG group compared with the placebo group. The scale 'Clinical Global Impression' was used as parameter of the improvement of the general state. The rate of 'improvement' was 52.9% for DNG and 22.9% for the placebo. The changes in QoL were assessed by using SF-36 Health Survey Questionnaire demonstrating a significant improvement of pain in the DNG group compared with the placebo group. The sum of the scores related to mental and psychological aspects improved in a similar manner with minimal differences between the two groups. The study concluded that DNG was superior to placebo in the improvement of pain symptoms.

Subsequently, the 168 women who had participated in the 12-week placebo-controlled study by Strowitzki *et al.* [44] were recruited for a study of long-term extension for the evaluation of pain control while using DNG to 2 mg/day for 53 weeks, for a total of 65 weeks adding the two studies [32]. The average VAS score in this population decreased progressively throughout the treatment period, from 56.9 mm (baseline placebo-

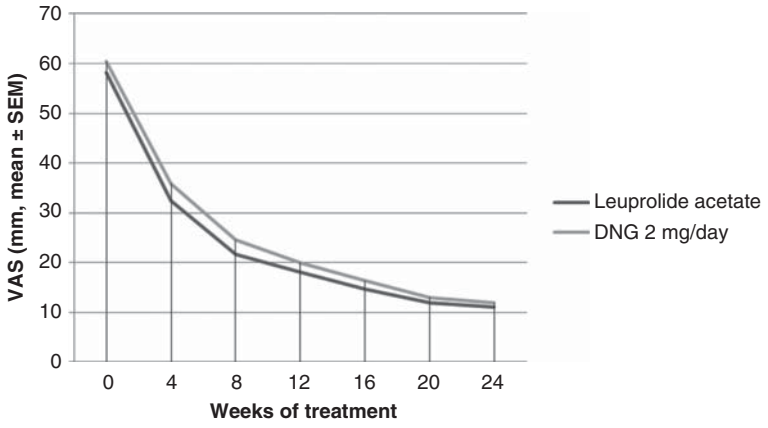

Figure 2. Noninferiority of DNG 2 mg/day versus leuprolide acetate for 24 weeks ($p < 0.0001$).
Reproduced with permission from [31].
DNG: Dienogest; SEM: Standard error of the mean; VAS: Visual analog scale.

controlled study) to 34.1 mm (baseline of the extension study long term), up to 11.5 mm at the end of treatment.

A 52-week, noncomparative, multicenter study was performed in Japan to test the long-term efficacy of DNG (2 mg/day) to define the safety evaluation of drug adverse reaction as primary end point. The study included 135 women and evaluated five subjective symptoms during nonmenstruation (lower abdominal pain, lumbago, dyschezia, dyspareunia and pain on vaginal examination) and two objective findings (induration involving the pouch of Douglas and limited uterine mobility). The incidence of drug adverse reactions in studied population was 88.9% (120/135 cases). The primary reactions consisted of metrorrhagia (71.9%), headaches (18.5%) and constipation (10.4%). Metrorrhagia was the most frequently found symptom, but it is seen that with the continuation of therapy there was a decrease in the intensity of the bleeding and the number of days of bleeding. In all the women in the study, bleeding was resolved with the end of treatment. They concluded that the long-term effect on BMD was small, whereas the effectiveness increased cumulatively [48].

6.3 Comparisons with GnRH-agonists

DNG at a dose of 2 mg/day was compared with leuprolide acetate (leuprolide acetate [LA], a GnRH analog administered at a dose of 3.75 mg intramuscularly every 4 weeks) in a randomized Phase III noninferiority trial. This study included 252 women with endometriosis confirmed by laparoscopy [31]. DNG and LA led to a continuous and comparable reduction of pelvic pain as measured by VAS. However, at the end of the 24 weeks, the reduction in the average VAS score was 47.5 mm for the DNG group and 46 mm for the LA group (95% CI: –9.26, 6.25). Therefore, the noninferiority of DNG compared with LA was demonstrated ($p < 0.0001$) (**Figure 2**). A similar improvement was also achieved by using the score B & B as a parameter for assessing the severity of symptoms and signs.

More recently, the same authors proposed a subsequent analysis of previous study to analyze the secondary efficacy and safety outcomes comparing DNG and LA in patients with endometriosis [49]. Study methods were the same of the previous trial. This study evaluated QoL, safety and tolerability. This evaluation was made through study of pain relief seen as reduction in VAS scales, B & B scores, impairment in daily activities, incidence of hypoestrogenic effects, irregular bleeding and impact on standard laboratory parameters. The conclusion of the study was that DNG was as effective as LA in treating the symptoms of endometriosis with QoL benefits and a favorable safety profile.

A Japanese randomized, double-blind, double dummy, multicenter, controlled study compared the administration DNG (1 mg b.i.d., 128 women) and intranasal BA spray (300 mcg three times a day, 125 women) for 24 weeks [50]. The results of this study were a reduction of the symptoms and signs in the two subgroups at baseline and after 24 weeks of treatment. Symptoms evaluated were low abdominal pain, lumbago, dyschezia, dyspareunia and pain on internal examination. Objective findings evaluated were induration in the pouch of Douglas and limited uterine mobility. The difference between two groups was not statistically significant except for the reduction in the score for the induration of the pouch of Douglas. Compared with BA, DNG was associated with irregular genital bleeding more frequently (95% in DNG group vs 67% in BA group) and with fewer hot flushes (50% in DNG group vs 67% in BA group). The reduction in BMD during DNG treatment was significantly lower than that during BA treatment ($p = 0.0030$).

A randomized, open-label, multicenter trial compared DNG (1 mg b.i.d. for 16 weeks) with triptorelin (3.75 mg intramuscularly every 4 weeks for 16 weeks) as consolidation therapy after laparoscopic surgery in 120 women with endometriosis [51]. In this trial, patients underwent a fist laparoscopy, which had a diagnostic, staging and therapeutic

purpose. Endometriosis was staged according to the rAFS and FOATI classifications both before and after this first laparoscopy. Subsequently, patients received DNG or triptorelin for 16 weeks and when medical therapies were discontinued they underwent a second laparoscopy with the aim of scoring endometriotic lesions according to rAFS and FOATI classifications. The difference between the changes in the implants score observed at second laparoscopy between the two groups after 4 months of treatment was not statistically significant ($p = 0.25$).

A recent meta-analysis [52] included two studies [31,50] that compared the efficacy and safety profile of DNG and GnRH analogs, one performed in Europe and the other in a Japanese population. The conclusion was that women in Europe and Japan respond in a similar manner in terms of pain relief after treatment with either DNG or GnRH analogs. DNG also showed equivalent effects on pain in both populations. However, there was heterogeneity in the changes of BMD.

6.4 Use of DNG following GnRH-agonists

Regarding the use of DNG as maintenance therapy after GnRH agonist to treat pelvic pain associated with endometriosis, we found only one study in the literature carried out in 2011 by Kitawaki *et al.* [53]. This prospective, nonrandomized clinical trial arises from the need to discontinue therapy with GnRH agonist because of the known side effects of prolonged treatment (maximum 6 months). Thus, the authors examined whether long-term administration of DNG following GnRH agonist therapy would prolong the relief of pelvic pain while reducing the amount of irregular uterine bleeding. Group G ($n = 38$) received GnRH agonist (leuprolide acetate or BA for 4 – 6 months and then DNG (1 mg/day) for 12 months). The dose of DNG was increased to 1.5 or 2 mg/day when the patient had uncontrollable uterine bleeding. Group D ($n = 33$) received only DNG (2 mg/day) for 12 months. Pelvic pain was assessed using a VAS. Uterine bleeding was semiquantified using a pictorial blood loss assessment chart (PBAC). There was no significant difference in pain reduction between group G and group D: dysmenorrhea ($p < 0.001$), nonmenstrual pelvic pain ($p < 0.01$) and dyspareunia ($p < 0.05$). The PBAC score during the first 6 months on DNG was significantly smaller in group G than in group D ($p < 0.01$). Therefore, the authors concluded that DNG long-term therapy maintains the relief of pelvic pain obtained with GnRH agonist and this regimen reduces the amount of irregular uterine bleeding that often occurs during the early phase of DNG therapy.

6.5 Efficacy in reduction of the lesions

Although pain relief is considered the primary efficacy measure in studies on endometriosis, some investigations assessed the changes in the size of the endometriotic lesions at laparoscopy after treatment with DNG.

The observation of a reduction of the lesions after use of DNG may suggest that this is not only a symptomatic drug.

One of the first studies showed a reduction of the lesions observed with second laparoscopy in 57 patients diagnosed with endometriosis who received DNG 1 mg b.i.d. for 24 weeks [54]. The second laparoscopy showed the disappearance of endometriotic lesions in 66.7% of women. Among the patients who still had endometrial lesions despite the therapy, a marked improvement was seen in 80.4% of women and no change in only 19.6%. Similar results were obtained in a subsequent study [55]. The study 'dose-finding' by Kohler *et al.* [43] also assessed the lesions reduction by the rAFS score. They showed that DNG at 2 mg and 4 mg/day results in a reduction of lesions after 24 weeks of treatment. The average rAFS score changed from 11.4 to 3.6 ($p = 0.0003$) in the 2 mg group and from 9.7 to 3.9 ($p < 0.0001$) in the 4 mg group. The severity of endometriosis according to the rAFS score decreased in both study groups. A multicenter, randomized trial including 142 women with stage II to IV endometriosis comparing DNG (1 mg b.i.d.) and triptorelin acetate (3.75 mg IM/month) for 16 weeks confirmed a reduction in the extent of endometriotic lesions. The rAFS score was initially 38 in both groups at baseline and dropped to 4 in both groups after 16 weeks [51]. Subsequently, another multicenter randomized trial comparing doses of 1, 2 or 4 mg DNG per day in two doses in 187 women diagnosed with endometriosis showed a decrease in the size of endometriotic cysts ($p < 0.05$) [46].

A very recent study clarified the impact of DNG on local histological events in humans that explain its therapeutic effect on endometriosis. The aim of this study was to evaluate the *in vivo* effect of DNG on endometriosis tissue. Endometrioma tissues from patients treated with DNG ($n = 7$) or not treated ($n = 11$, controls) were collected. This study demonstrates that endometrioma taken from patients treated with DNG show remarkable histological features such as reduction of proliferation measured with Ki67 ($p < 0.05$), aromatase expression ($p < 0.05$) and angiogenesis ($p = 0.20$), and increase of apoptosis ($p < 0.05$) [56].

7. Safety and tolerability

The most frequent adverse effects seen during long treatment (52 weeks) with DNG at 2 mg/day in 135 women were headache (18.5%), constipation (10.4%), nausea (9.6%), hot flushes (8.9%), weight gain (8.1%), dizziness (5.9%) and breast tenderness (5.9%) [48]. In an analysis of four clinical trials that collected 332 cases, the most commonly reported adverse events in women treated with DNG 2 mg/day were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%) and acne (5.1%) (**Table 2**) [22].

The most common side effect is abnormal uterine bleeding, which is more frequent during the first few weeks of DNG use and decreases with continued treatment [48,57]. In the long-term use of DNG (52 weeks at 2 mg/day), 97/135 patients

Table 2. Incidence of adverse reaction to DNG in different studies.

	Duration of treatment (weeks)	Dosage of DNG (mg/day)	Number of patients	Type of study	Adverse drug reactions n (%)									
					Abnormal uterine bleeding	Headache	Constipation	Nausea	Weight gain	Hot flushes	Breast discomfort	Acne	Depressed mood	Dizziness
Medicines Evaluation Board (Netherlands) [22]	-	2	332	Medicines evaluation board	-	30 (9.0%)	-	-	-	-	18 (5.4%)	17 (5.1%)	17 (5.1%)	-
Strowitzki *et al.* [31]	24	2	120	Randomized, double-blind, multicenter, open-label trial	-	15 (12.5%)	-	-	8 (6.7%)	0	-	5 (4.1%)	6 (5.0%)	-
Strowitzki *et al.* [44]	12	2	102	Randomized, double-blind, placebo-controlled trial	-	11 (10.8%)	-	3 (2.9%)	-	-	2 (2.0%)	-	2 (2.0%)	-
Momoeda *et al.* [48]	52	2	135	non-randomized, long-term treatment, multicenter trial	97 (71.9%)	25 (18.5%)	14 (10.4%)	13 (9.6%)	11 (8.1%)	12 (8.9%)	8 (5.9%)	-	-	8 (5.9%)
Harada *et al.* [50]	24	2	129	Randomized, double-blind, multicenter, controlled trial	122 (95%)	32 (25%)	-	-	-	64 (50%)	-	-	-	-
Cosson *et al.* [51]	16	1	59	Prospective, multicenter, randomized trial	36 (61.6%)	-	-	-	-	6 (9.6%)	-	-	-	-

-: Not mentioned in the study; DNG: Dienogest.

Table 3. Bleeding patterns in women treated with DNG 2 mg/day [22,31,32,44,57].

Bleeding patterns	First 90 days of treatment (total number = 290). no. (%) [31,32,44]	Fourth 90 days of treatment (total number = 149). no. (%) [32]
Amenorrhea	6 (2%)	42 (28%)
Infrequent bleeding	78 (27%)	36 (24%)
Frequent bleeding	38 (13%)	4 (3%)
Irregular bleeding	101 (35%)	33 (22%)
Prolonged bleeding	110 (38%)	6 (4%)
Normal bleeding	55 (19%)	33 (22%)

Data are presented as number of patients and percentage.
Adapted from Visanne® Product Monograph [65].
DNG: Dienogest.

(71.9%) reported metrorrhagia, but in 96 of these cases the symptom disappeared during treatment or 2 months after end of treatment with a median number of days of genital bleeding per 28 days of treatment period of 21 days at 5 – 8 weeks, 9 days at 21 – 24 weeks and 2 days at 49 – 52 weeks of treatment, indicating a decrease in abnormal bleeding as the treatment period was extended. The abnormal bleeding during therapy with DNG is caused by endometrial regression (breakthrough bleeding) due to a continuous duty, which results in different bleeding pattern ranging from spotting to irregular bleeding. In patients treated with 2 mg/day of DNG up to 52 weeks (Phase III trials), in the first 90 days of therapy the bleeding pattern was prolonged bleeding (38%), irregular bleeding (35%) and infrequent bleeding (27%), frequent bleeding (13%) and amenorrhea (2%). In the fourth 90-day therapy, the bleeding pattern were changed as follows: amenorrhea (28%), infrequent bleeding (24%), frequent bleeding (3%), irregular bleeding (22%) and prolonged bleeding (4%) (**Table 3**) [22,31,32,44,57]. The period chosen was 90 days in accordance with the reference range proposed by the WHO [58].

As already shown in preclinical studies, DNG has low activity for androgen receptors and it has also some antiandrogenic activity [21,59], which explains the limited androgen-like adverse effects like weight gain, acne, alopecia and hirsutism.

One of the features that makes DNG so effective in the treatment of endometriosis is the fact that it creates a hypoestrogenic climate at the level of endometrial tissue without, however, excessively decreasing plasma E2 concentration, which tends to stabilize at the lower limit of the normal range of concentration [50]. Klipping *et al.* [29] assessed the minimum dose of DNG inhibiting ovulation by randomizing 102 participants to receive 0.5, 1, 2 or 3 mg/day of DNG. The results of this study showed that complete ovulation inhibition was observed at DNG doses ≥ 2 mg/day and was rapidly reversed after treatment cessation. Besides they showed that 2 mg DNG achieves a decrease in E2 concentration sufficient to reduce estrogen-dependent disease, combined with a systemic E2 exposure that minimizes hypoestrogenic side effects and likelihood of bone loss. This is an important advantage in terms of adverse effects from hypoestrogenism, especially when compared with GnRH analogs. Twenty-four weeks of treatment with DNG (2 mg/day orally) decrease mean E2 levels by only 6.4 pmol/l compared with 240.5 pmol/l in patients treated with LA (3.75 mg, depot intramuscolar injection, every 4 weeks) at the end of treatment (**Figure 3**) [31]. In a 12-week placebo-controlled study, E2 decreased by 70 ± 282 pmol/l [44]; the mean E2 levels showed minimal changes during continuous treatment with DNG for 53 weeks [32]. In agreement with these observations, DNG does not cause significant hypoestrogenic adverse effects such as reduction of BMD, vaginal dryness, hot flashes, decreased libido and sleep disturbances [31]. In particular, in the patients treated with DNG, hot flushes occur with a mean of 0.89 days per week of treatment, whereas in patients treated with LA they occur for an average of 23.4 days per week. Furthermore, the frequency of this symptom remains low during treatment with DNG, whereas it tends to increase during treatment with LA. A further study comparing DNG (1 mg b.i.d.) and triptorelin acetate (3.75 mg/month intramuscularly) for 16 weeks showed a significantly lower incidence of hot flashes in the DNG group (9.6 vs 61.2%) [51].

Twenty four weeks of treatment with DNG do not significantly change BMD, whereas LA causes a significant reduction in BMD at the lumbar spine [31]. This observation is confirmed by the changes of bone reabsorption markers (measured with urine calcium levels and urinary Cross-Laps levels) in patients treated with LA group versus no significant change in those treated with DNG.

DNG does not have adverse effects on lipid metabolism. This was also confirmed by a study that analyzed the safety of DNG at high dose (20 mg/day) for 24 weeks [60]. In the study comparing DNG and placebo for 12 weeks, the levels of plasma lipids (such as LDL, HDL and triglyceride) showed little change in both groups [44]. When compared with LA for a 24-week treatment, no clinically relevant change in lipids levels was observed in both treatment groups [49].

DNG does not appear to have significant effects on carbohydrate metabolism. In the dose-finding study of 24 weeks, there was no significant change in blood glucose in any patient [43]. The treatment with progestins may facilitate

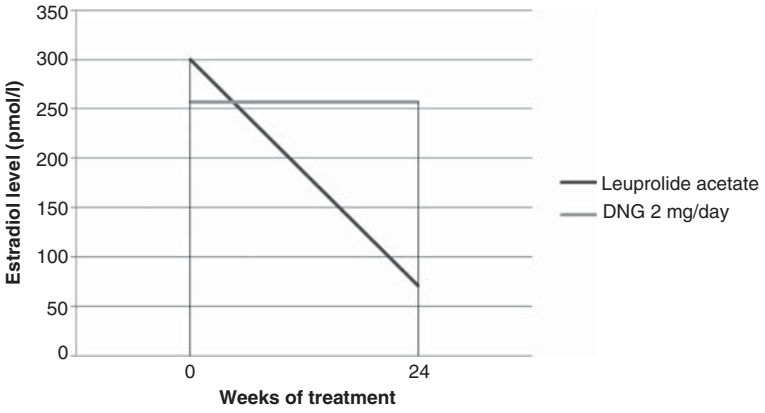

Figure 3. Sieric estradiol levels by using DNG 2 mg/day or leuprolide acetate for 24 weeks.
Reproduced with permission from [31].
DNG: Dienogest.

weight gain. No significant change in weight has been reported in patients treated with DNG 2 mg/day for 12 weeks when compared with placebo [44]. The long-term study [32] showed that only a minimal change in body weight (+0.58 kg) occurred after 1 year of treatment with DNG.

8. Conclusion

DNG combines the advantages of 19-nortestosterone derivatives with the benefits of progesterone derivatives. DNG has a good pharmacokinetic profile with an absorption of 90.5% when taken by mouth, half-life that is suitable for the dosage of one administration per day and a limited influence from the food on the absorption. The marked tropism of DNG *in vivo* against the endometrial tissue explains its effectiveness in the treatment of endometriosis. The mechanism of action in endometriosis arises from the fact that the DNG inhibits the secretion of gonadotropins with decrease in the endogenous release of estradiol (which, however, stabilizes at levels that do not induce adverse effects of estrogen deficiency), thus creating a hypoestrogenic and hyperprogestinic endocrine environment that induces initial decidualization and subsequent atrophy of endometriotic lesions. In addition, DNG has strong antiandrogenic activity, whereas it has no glucocorticoid and mineral corticoid effects. The efficacy of DNG was also demonstrated by the clinical point of view with a trial that has shown the superiority of DNG compared with placebo in reducing the pain associated with endometriosis. Furthermore, DNG was compared with the reference treatment for endometriosis represented by GnRH agonists demonstrating noninferiority of DNG compared with these compounds with a lower incidence of adverse effects (especially hypoestrogenic effects), both as regards the improvement of the symptom pain and as regards the reduction of endometriotic lesions diagnosed at laparoscopy. DNG is a well-tolerated drug with a rate of treatment discontinuation due to adverse effects < 5%. The most common adverse effects were abnormal uterine bleeding, headache, breast discomfort, depressed mood and acne, while not going to significantly change body weight, BMD and lipid profile in the blood of women. Abnormal bleeding, generally well tolerated by women, tends to decrease with continued treatment.

9. Expert opinion

Although the European Society of Human Reproduction and Embryology (ESHRE) explains that the cure of symptomatic endometriosis can involve analgesics, hormones, surgery, assisted reproduction or a combination of approaches, endometriosis treatment today is mostly made up of empiric therapy with analgesics and hormonal therapy based on a diagnosis of suspicion [61]. The treatment should be efficacious, but it should also be the least expensive and with minimal risks. Hormonal therapies (GnRH agonists, danazol, gestrinone, combined oral contraceptives and medroxyprogesterone) have similar efficacy, but differ in their adverse effects and costs. GnRH agonists (such as leuprorelin acetate, BA and triptorelin) are currently considered the most effective drugs in relieving pelvic pain associated with endometriosis [7], but they cause many adverse effects related to the hypoestrogenism (hot flushes, bone mineral depletion, mood swings, vaginal dryness). Therefore, GnRH agonists are not recommended for continuous use for a period of time that exceeds 6 months of treatment because of the potential depletion of the bone mass. The use of an add-back therapy, which adds an estrogen, progestin or estrogen–progestin combination, allows to reduce the adverse effects of estrogen deficiency and to extend the duration of the treatment, but this leads to an increase in costs. Hyperandrogenic compounds cause adverse androgen-like effects (acne, seborrhea, hirsutism, alopecia and weight gain) in addition to make an unfavorable change in the levels of cholesterol in the blood (increased

LDL-cholesterol and decrease HDL-cholesterol) [8]. Systematic reviews of the literature have shown limited evidence in favor of the efficacy of low-dose combined oral contraceptives in relation to the pelvic pain associated with endometriosis [62,63], although some trials have demonstrated their superiority over placebo [64]. They have also been shown to be effective as GnRH analogs [62]. However, hormonal contraceptives are widely used for their advantages, including some contraceptive protection, long-term safety, low cost and control of menstrual cycle. Progestins are used today as one of the options for treatment of endometriosis. Among these agents, the most widely used are NETA 2.5 – 5.0 mg/day and the Lng-IUD. They allow a long-term treatment of endometriosis, although they may cause some adverse effects such as headaches, weight gain, androgenic effects (especially for derivatives of 19-nortestosterone) and reduced BMD.

Thanks to these features that combine excellent efficacy in reducing pain and symptoms associated with endometriosis and in reducing the size of endometrial lesions with good tolerability of the product in the long term, the DNG has been proposed as the progestin in the reference treatment of endometriosis. In addition, DNG long-term therapy has also proven effective in maintenance therapy after use of GnRH agonists [53]. Further studies with large sample size are needed to confirm its good clinical efficacy and tolerability. However, some issues remain unsolved. In fact, as DNG causes inhibition of ovulation, it does not solve the problem of infertility associated with endometriosis. Moreover, this is still an open issue as currently there are no hormonal therapies ensuring an improvement in infertility associated with endometriosis. On the other hand, no study investigated the potential of contraceptive effect of DNG; therefore, this therapy should be associated with other methods of contraception (e.g., barrier methods). Finally, a further limitation of the use of DNG as daily therapy in the long term is that the cost of the therapy is higher than other progestins available on the market and combined oral contraceptives. Future studies should compare the efficacy and safety of DNG with other progestins.

Declaration of interest

S Stefano has had financial relationships (lecturer or member of advisory board) with Pfizer and Astellas. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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