Norethisterone and its acetate – what's so special about them?

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ABSTRACT

Introduction Progestogens (progestins) are widely used for contraception, in postmenopausal hormone therapy, and in treatment of abnormal uterine bleeding and endometriosis. Norethisterone (NET) and its acetate (NETA) differ from other progestogens by their partial conversion to ethinylestradiol (EE). We review their special characteristics and focus on the clinically relevant risk factors associated with estrogen action, such as migraine with aura and risk of thrombosis.
Methods Narrative review based on a medical literature (OvidMedline and PubMed) search.
Results NET converts to significant amounts of EE; 10–20 mg NET corresponds to 20–30 µg EE. The effects of NET on the endometrium are pronounced, making it a good choice for treating abnormal uterine bleeding, endometriosis, and endometrial hyperplasia. NET also has beneficial effects on bone mineral density and positive or neutral effects on cardiovascular health. Conversely, long-term use of NET is associated with a slightly increased breast cancer risk, and the risk of venous thromboembolism is moderately increased. This risk seems to be dose-dependent; contraceptive use carries no risk, but therapeutic doses might be associated with an increased risk. Studies suggest an association between combinations of EE and progestogens and ischaemic stroke, which in particular concerns women with migraine. No studies have, however, assessed this risk related to the therapeutic use of NET.
Conclusions NET is a potent progestogen, especially when considering the endometrium. Its partial conversion to EE, however, is important to remember. Clinical consideration is required with women at high risk for either breast cancer or thromboembolism, or experiencing migraine with aura.

Key message points

- Norethisterone (NET) converts in part to ethinylestradiol (EE); 10–20 mg NET equals 20–30 µg EE.
- NET has a strong influence on the endometrium and it is a good option for treatment of endometrial hyperplasia.
- Special consideration is needed in cases of high risk for thromboembolic events and when treating women experiencing migraine with aura.

INTRODUCTION

Progestogens (progestins) are synthetic analogues of progesterone, and are widely used for contraception, postponing menstruation, as part of postmenopausal hormonal therapy (HT), and for the treatment of abnormal uterine bleeding and endometriosis. Although all progestogens imitate natural progesterone, each progestogen also has its individual characteristics based on the different pharmacokinetic and pharmacodynamic characteristics, namely different binding affinities to estrogen, androgen, and glucocorticoid and mineralocorticoid receptors.[1] The availability and use of different progestogens vary globally.

Norethisterone (NET) (and similarly norethisterone acetate, NETA, and norethindrone) is the most widely used progestogen in several European countries. It is an effective progestogen with a strong endometrial effect.[2] In contrast to other progestogens, NET partly converts (approximately 0.4%–1%) to ethinylestradiol (EE) in the liver, therefore also causing estrogenic effects in the body.[3 4] As preceding estrogen action is needed for progestogen activity, the resulting EE also strengthens the progestogenic properties of NET. However, considering the thromboembolic risk associated with EE,[5] this conversion might be of importance concerning the possible adverse effects of NET(A).

The purpose of this review is to assess the specific beneficial and potentially negative effects of NET, and to consider their implications for clinical use. We especially wanted to focus on certain risk groups such as women at higher risk for thromboembolic events and migraine with aura, typically considered as contraindications for the use of EE.

METHODS

We used Ovid Medline and PubMed to find studies and reviews on norethisterone. We used the search terms progest*, NETA, norethisterone, norethisteron*, and norethindron*, individually and in combination with ethinyl estradiol/EE and included only articles in English. Additional search terms were thromboembol*, thrombo*, breast cancer, endometr*, glucose metabolism, bone, and psychologic* in conjunction with NET*.

PROGESTOGENS

In the early 1900s, scientists strived to find a means of ovulation inhibition. Natural, orally administered progesterone had poor efficiency; and finally in 1951, the first synthetic progestogen, norethisterone, was created by Carl Drejassi from natural testosterone. The approach involved the removal of a methyl group from C19 of testosterone, converting an androgenic molecule to a progestogenic one. Moreover, the addition of an ethyl group to C17 resulted in significantly increased absorption from the gastrointestinal canal. This key invention changed the field of contraception and steroid research.[6]

Progestogens can be classified according to their time of discovery or chemical structure.[1] They are chemically classified according to the precursor molecules into 19-nortestosterone (estranes and gonanes) and 17-α hydroxyprogesterone derivatives (pregnanes), and others (eg, drospirenone derived from spironolactone)(table 1).

Progestogens can also be grouped into different generations according to their order of discovery, especially when discussing the thrombotic effects of different progestogens in combination with estrogen for contraception. The second-generation progestogens (eg, levonorgestrel) display the lowest risk of thromboembolic complications, and the third (eg, gestodene and desogestrel) and fourth (eg, drospirenone) generations the highest.[7–10]

All progestogens have a slightly different clinical profile based on their distinctive ability to bind to cellular steroid receptors, namely estrogen, androgen, progesterone, glucocorticoid, and mineralocorticoid receptors. Additionally, they differ in their pharmacokinetic characteristics. For example, the absorption of 19-nortestosterone derivatives (such as NET) from the gastrointestinal tract is effective, whereas that of natural progesterone is less complete. Some progestogens (eg, desogestrel) are prodrugs, and are effective

Table 1 Pharmacology and biological activity of progesterone and synthetic progestogens (adapted from Schindler et al)[1]

	Progestogen	Progestogenic	Antigonadotropic	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Antimineralocorticoid
	Progesterone	+	+	+	–	–	+/–	+	+
	Medroxyprogesterone acetate (MPA)	+	+	+	–	+/–	–	+	–
	Dydrogesterone	+	–	+	–	–	+/–	–	+/–
First generation	Norethisterone (NET)	+	+	+	+	+	–	–	–
	Lynestrenol*	+	+	+	+	+	–	–	–
Second generation	Cyproterone acetate	+	+	+	–	–	++	+	–
	Levonorgestrel	+	+	+	–	+	–	–	–
Third generation	Desogestrel	+	+	+	–	+	–	–	–
	Norgestimate†	+	+	+	–	+	–	–	–
	Gestodene	+	+	+	–	+	–	+	+
Fourth generation	Drospirenone	+	+	+	–	–	+	–	+
	Nomegestrol acetate	+	+	+	–	–	+/–	–	–
	Dienogest	+	+	+/–	+/–	–	+	–	–

*Prodrug.
†Approximately 22% converts to levonorgestrel.[11]

only following conversion by first-pass metabolism to an effective compound (3α-ketodesogestrel, that is, etonogestrel). Progestogens bind to serum proteins such as sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG), and albumin. In addition, individual differences in metabolism can multiply the differences in their serum concentrations up to five-fold.[11]

Therefore, the equivalent progestogen doses needed for ovulation inhibition and endometrial transformation vary. The doses required, especially for endometrial transformation, are also somewhat unclear, and rely mainly on preclinical studies. Moreover, few randomised studies have compared the characteristics of different progestogens.[12] The influences of administration route and possible combination with an estrogen component further complicate these comparisons.

NORETHISTERONE
NET was the first synthesised and clinically used progestogen. It has strong progestogenic characteristics as well as tissue-specific androgenic, antigonadotropic, anti-estrogenic, and estrogenic features following the high binding affinity of NET and its metabolites to the corresponding steroid receptors.

Therapeutic indications of NET include abnormal uterine bleeding, endometriosis, and postponing menstruation. It is also widely used in contraception, alone and in combination with EE, and for alleviation of postmenopausal symptoms in HT, combined with an estrogen component. The dose varies by indication: in therapeutic use it is typically 10–15 mg/day, in HT 0.5–1 mg/day, and in contraceptive use 0.35 mg/day.

NETA is quickly absorbed from the gastrointestinal tract and converted to the active form NET by removal of the acetate group.[13] Following absorption, NET binds partly to SHBG (36%) and mainly to albumin (61%). The non-protein-bound fraction of NET in circulation is 3%–4%.

It is noteworthy that lynestrenol, a progestogen widely used for treatment of endometriosis and therapeutic amenorrhea, is also a prodrug of NET. Although smaller doses seem to have a lower conversion rate, 5 mg of lynestrenol corresponds to approximately 5 mg NET.[14]

The partial conversion to EE, a specific feature of NET, had already gained attention some decades ago. In 1997, Kuhnz et al studied 24 postmenopausal women in a single-dose crossover study and measured NET and EE concentrations after oral administration of 5 or 10 mg NETA, or 5 mg NET.[3] They discovered that 1 mg NETA was converted to approximately 6 μg EE. The conversion rate for NET was approximately 25% lower. Based on the simultaneous increase in circulating NETA/NET and EE, the authors proposed the conversion to occur mainly in the liver. Hypothetically,

the androgenic activity of NET might partly compensate the effects of EE in the liver.

Later in 2007, Chu et al conducted a study on 20 premenopausal women, randomised to receive either 10, 20, or 40 mg NETA for 7 days in the follicular phase of the menstrual cycle.[4] The conversion rate of NETA to EE was estimated to be at least 0.14 %, but even up to 0.20%–0.33%. For comparison, ingestion of 30–40 μg EE leads to a plasma concentration of 100–135 pg/mL, whereas the EE concentration following 10 mg NETA was 58 pg/mL, and following 20 mg NETA 178 pg/mL. Thus, the intake of 10–20 mg NETA equals the net effect of a combined hormonal contraceptive (CHC) pill containing 20–30 μg EE. This amount is likely to be clinically significant, especially in women at increased risk for thromboembolism or with other contraindications to exogenous estrogens.

CLINICAL EFFECTS OF NETA
Table 2 summarises the clinical and metabolic effects of NET and NETA.

Endometrium
During the menstrual cycle, the estrogen-primed endometrium is converted from proliferative to secretory histology following exposure to progesterone. The therapeutic use of progestogens utilises this property, and includes indications such as treatment of abnormal uterine bleeding, induction of therapeutic amenorrhea, and postponing menstruation. Additionally, progestogens are effective in treating endometriosis. The typical daily dose of NET used for controlling uterine bleeding is between 10 and 20 mg, in comparison to the 0.5–1 mg required for ovulation inhibition in CHCs and the 0.35 mg used in progestogen-only contraceptives.

NET has a pronounced effect on the endometrium.[2] The dose needed for endometrium transformation is 30–60 mg per cycle—significantly less than the commonly used daily dose of 10–15 mg for 10 days.[1] In postmenopausal HT, transdermal NET in combination with estradiol also appears to be effective; the risk of endometrial hyperplasia was undetectable following sequential administration of 140–400 μg/day NET and in continuous treatment with 170–350 μg/day.[15] When compared with MPA in a randomised controlled trial (RCT), the daily use of 1 mg NET resulted more often in endometrial atrophy (73%) than treatment with 2.5 mg MPA (32%).[2] In the treatment of endometrial hyperplasia, daily doses of 15 mg NET, 10 mg MPA, and 15 mg lynestrenol (10 days/cycle) were equally effective.[16] In continuous combined postmenopausal HT, the use of NET seems to result in the lowest rate of dysfunctional bleeding.[17]

Risk of thrombosis
The estrogen component of CHCs was long suspected to be the main culprit for the associated

Table 2 Clinical and metabolic effects of norethisterone (NET) and norethisterone acetate (NETA)

Heading	Relative potency	Remarks	References
Endometrium	+++	A potent progestogen	2 15–17
Thrombosis	–/++	Dose-dependent increase in the risk of thrombosis ► No risk in doses (ie, 0.35 mg/day) used in progestogen-only contraceptive pills ► Slightly elevated in doses (ie, 0.5–1 mg/day) used in HRT with oral estrogen ► Significant elevation in therapeutic use (ie, 10–15 mg/day)	5 7 18 19 21 22 50
Breast	+	Stimulates proliferation of breast cancer cells in vitro Cancer risk increased after 5 years' use	25–27
Bone	++	Dose-dependent increase in bone mass and density	29–32
Cardiovascular health			
Lipids	+	Lowers HDL, but also LDL and triglycerides maintaining a beneficial ratio	34
Glucose	Neutral?	Paucity of data and no data on patients with type 1 and 2 diabetes	31 35 36
Body composition	+	Decrease in visceral adiposity, but only results concerning HRT together with estrogen component	37 38
Cognitive function and mood	+/–	Inconclusive results	40–43

HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein.

thromboembolic complications. The progestogenic component, however, plays an additional role in modifying this risk. According to a meta-analysis, the second-generation progestogens, such as levonorgestrel, in combination with EE demonstrate the lowest risk of thrombosis (risk ratio (RR) 2.8 compared with non-use). For the first-generation progestogens, such as NET, the corresponding RR is 3.2, and for the third- and fourth-generation progestogens the RR is 3.8.[7]

When comparing progestogen-only contraceptives, none of the studied compounds activated the hemostatic system or increased the risk of venous thromboembolism (VTE).[18] A recent systematic review evaluated the thromboembolic risk of progestogen-only contraception in high-risk groups such as smokers, women with hypertension, or with a family history of thrombosis, and found no increased risk of VTE with any of the progestogens studied. The use of injectable MPA, however, surprisingly increased the risk of VTE (odds ratio (OR 3.0).[19] The reason for this remains unclear. Hypothetically, women using injectable contraception might have a common underlying feature increasing their susceptibility to VTE.

In postmenopausal HT, the type of estrogen and its administration route additionally influence the thrombotic risk. The transdermal route of HT administration is associated with lower risk, and oral estradiol is associated with a lower risk compared with oral conjugated equine estrogen (CEE). When comparing oral NET and MPA with similar estrogen dose and route of administration, NET showed a slightly higher risk of VTE.[20] The use of transdermal estrogen, even when combined with progestogens, failed to elevate the risk.[5]

The World Health Organization (WHO) collaborative study[21 22] assessed the risk of VTE associated with therapeutic use of progestogens, typically used in higher doses than in contraception. Although the number of patients was limited, the study suggested that progestogen therapy is associated with an elevated VTE risk. The characteristics of women using therapeutic progestogens and the underlying conditions might naturally influence this risk. However, after adjusting for cardiovascular disease, diabetes, and smoking, the risk of VTE remained increased (OR 5.9). Furthermore, a register-based study[22] evaluated the VTE risk associated with contraceptive and therapeutic use of progestogens, and demonstrated an increased VTE risk during therapeutic (RR 5.3 (1.5–18.7)), but not during contraceptive, use (RR 1.3 (0.3–6.8)) of progestogens. Unfortunately, neither of these studies performed subgroup analysis according to the type of progestogen.

In conclusion, contraceptive use of NET in combination with EE seems to slightly increase the risk for VTE compared with second-generation (ie, levonorgestrel-containing) CHCs. Preparations for postmenopausal HT containing NET and transdermal estradiol do not show such an increase. However, in progestogen-only therapy the possibly increased thrombogenic profile of NET requires attention. Thus, concerning the risk of thrombosis, it has been suggested that therapeutic doses of NET should be considered similar to CHCs containing both estrogen and progestogen.[23]

Breast cancer

The risk of breast cancer is a common concern during the use of HT for menopausal symptoms. This increased risk has been associated especially with the progestogen component of HT, increasing with longer duration and continuous progestoen intake.[24]

When comparing the effects of NETA, MPA, and dienogest in vitro, either alone or in combination with estradiol, they similarly stimulated the growth of cancer cells. Conversely, dydrogesterone, tibolone, and natural progesterone stimulated apoptosis.[25] When tested in vivo and evaluated using fine-needle biopsies from breast tissue, 3 months' use of 1 mg NET in combination with 2 mg estradiol resulted in a four-fold increase in breast cell proliferation. A similar increase was detected when using dienogest in combination with estradiol.[26]

In a Finnish register-based study, however, there was no increased risk of breast cancer after 3 years of HT use, but the risk was significantly increased after 5 years of use.[27] Lower risk was detectable among users of sequential HT compared with continuous use of progestogen. Additionally, the breast cancer risk was significantly higher among users of NETA (standardised incidence ratio (SIR) 2.03) compared with that of MPA (SIR 1.64). However, these results are from large observational studies and to our knowledge there are no RCTs comparing different progestogens.[28]

Bone

Bone density is strongly associated with female hormones as estrogen reduces bone remodelling and resorption, and maintains bone formation. In a placebo-controlled trial, the use of NET together with estradiol resulted in increased forearm bone mass and spinal bone mineral density (BMD).[29] This effect was dose-dependent and related to both the estrogen and NET doses.

The use of NETA was also associated with decreasing markers of bone resorption and maintaining similar bone formation parameters further suggesting the stimulatory effect of NETA on bone formation.[30] In a 6-month study comparing HT with NETA/estradiol, tibolone, and MPA/CEE, all regimens resulted in similar positive effects on BMD.[31] However, a recent 2-year follow-up study suggested that compared with MPA, NETA has a more pronounced effect on BMD and fracture protection.[32]

Cardiovascular health and metabolism

Overall, the incidence of cardiovascular disease is lower among women before menopause than among men. This presumably relates to estrogen, which improves lipid balance, body composition, insulin resistance, and endothelial function, as well as reducing coagulation and inflammatory response.[33]

After menopause, progestogens in HT seem to antagonise the positive influence of estrogen on cardiovascular health. The androgenic and estrogenic properties of NET result in a combined outcome lowering both high-density lipoprotein (HDL) and low-density lipoprotein (LDL), as well as triglycerides, but maintaining the HDL/LDL ratio.[34] When comparing different progestogens, progesterone, dydrogesterone, and nomegestrol acetate have neutral effects on lipids;

drospirenone has positive effects, whereas the results concerning MPA are still controversial.[34]

Less is known about the effects of progestogens on glucose metabolism, although it seems rather neutral. A recent review on CHCs containing different combinations of estrogens and progestogens concluded that studies are small, are performed often in a healthy normal-weight population, and thus the results remain inconclusive.[35] Few studies are suggestive of NET having a neutral or favourable effect on glucose regulation.[31 36] Additionally, there is a paucity of studies evaluating the metabolic effects of progestogens among women with pre-existing diabetes or other conditions with marked insulin resistance such as polycystic ovary syndrome.

In addition to lipid and glucose metabolism, body composition also relates to cardiovascular health. The use of HT seems to inhibit the age-related increase in body fat percentage and to decrease the deposition of metabolically more active visceral adipose tissue.[37 38] These effects did not differ between women using HT preparations containing either NETA or MPA.[39]

In conclusion, NET seems to have neutral or favourable effects on cardiovascular health.

Cognitive function and mood

The use of gynaecological hormonal therapies has been associated with psychological side effects such as mood swings, anxiety, and depression, and the biggest culprit has been the progestogen component. The Women's Health Initiative (WHI) study raised a concern about possible negative effects of HT on cognitive function; the effects of progestogens on memory and mood seem to depend on the timing of exposure and the age of the woman.[40] HT with NET and estradiol valerate showed only minor effects on memory and attention,[41] whereas an another study demonstrated more activation in the visual memory cortex in users of NET and EE.[40] An RCT assessing HT with either NETA, MPA, dydrogesterone, or nomegestrol acetate in combination with estradiol found that none of these progestogens had an effect on depression. However, the use of preparations containing dydrogesterone and MPA reduced anxiety.[42] Another placebo-controlled study assessed symptoms typical of premenstrual syndrome and showed that NETA in combination with estradiol had a dose-dependent effect on increasing depression, anxiety, and irritability.[43] Ultimately, the results concerning the psychological side effects of NET remain inconclusive.

CLINICAL IMPLICATIONS FOR WOMEN WITH RISKS RELATED TO THE USE OF EXOGENOUS ESTROGEN

Migraine

Migraine is a common neurological disorder affecting approximately 15%–18% of women of fertile age in Europe and North America. The occurrence of migraine attacks is often hormone-related. Altogether 10%–15% suffer from 'classic migraine' with a related aura. Aura

refers to a variety of neurological symptoms occurring before the onset of headache, such as visual disturbances or even numbness, tingling, or weakness on one side of the body, lasting for a maximum of an hour. Migraine with aura (MwA) is associated with a 2-fold risk of stroke. Having more than 12 auras annually further increases this risk (OR 10.4).[44]

MwA is an established contraindication to the use of CHCs. Weak evidence suggests a 2- to 4-fold higher risk of stroke among women with MwA and CHC use, but studies have not differentiated between the distinct steroidal compounds.[45] According to a recent register-based study, common migraine is also associated with an elevated stroke risk, but it is lower than that associated with MwA. The use of CHCs among women with MwA increased the risk even further (OR 6.1).[46] A Cochrane review demonstrated an increasing risk of stroke with increasing EE doses: lowest risk (OR 1.6) was associated with the use of 20 μg EE-containing preparations and the highest (OR 2.4) with the use of 50 μg or more EE.[47] No studies have evaluated this risk related to low-dose EE combinations, and according to the adjacent progestogen compound.[44] Conceivably, they might be similarly safe. Hypothetically, continuous delivery of hormones (eg, by a vaginal ring) might reduce the occurrence of auras and consequently lower the risk of stroke. There is, however, no scientific evidence to support this hypothesis.[48]

Although the evidence supporting the association of ischaemic stroke and EE is rather weak, most studies suggest an increased risk. Progestogen-only contraceptive pills containing NET might be considered safe due to their low dose. However, there are no studies concerning the therapeutic use of NET in which higher doses, such as 10 mg/day, are used. We suggest that the resulting circulating EE requires clinical consideration before prescribing NET to women with MwA for long-term use.

Higher risk for thromboembolic events

History or increased risk of VTE is an established contraindication to CHCs but not to progestogen-only contraception.[18] Among HT users, the risk of VTE is higher in women using NET compared with women using MPA.[20] However, the risk of thrombosis is seldom considered when prescribing therapeutic doses of progestogens, and to our knowledge, there are no studies evaluating the effects of therapeutic NET doses on VTE risk.

Nevertheless, due to the special characteristics of NET(A), we propose that the individual risk of thrombosis should be considered when prescribing NET(A) for therapeutic purposes. One group requiring special attention is obese women who are simultaneously at high risk for both endometrial hyperplasia and VTE. Among women at increased risk of thrombosis, alternative progestogens should be considered, and for example the levonorgestrel intrauterine system (LNG-IUS) could be a safe and highly effective option.[49]

Women at risk for breast cancer

In vitro and in vivo studies have demonstrated the stimulatory effect of NET on breast cancer cells.[25][26] Also, in long-term follow-up the use of NET has resulted in a higher risk of breast cancer.[27] Although there are no solid data, short-term use is likely to be safe, but for long-term use, alternative progestogens might offer a better alternative.

CONCLUSIONS

Considering the numerous progestogens available, there are several good options for contraception, postmenopausal HT, and therapeutic use. Even though NET was the first synthetic progestogen used clinically, it still holds its place as a potent and useful progestogen. In brief, NET is potentially the most efficient progestogen regarding the endometrial effect.[2][15–17] It has beneficial effects on BMD[29–32] and minimal effects on glucose[31][35][36] and lipid metabolism.[34]

Some characteristics of NET, however, should be acknowledged. In particular, the partial conversion to EE requires special attention[3][4] due to the potential related complications, such as VTE and stroke in certain risk groups.

The risk for VTE might be increased especially with therapeutic doses[21] and among women at higher intrinsic risk for thromboembolic events. In HT with transdermal estrogen the risk for VTE is not increased; but in combination with oral estradiol, the odds for VTE are higher with NET than MPA.[20] EE increases the risk of stroke among women with MwA even further, which should be taken into account before prescribing therapeutic doses of NET for these women. Special consideration is also needed when prescribing therapeutic doses of NET to

Additional Educational Resources

▶ Stanczyk FZ. All progestins are not created equal. *Steroids* 2003;68(10–13):879–90.

▶ Schindler AE. Differential effects of progestins on hemostasis. *Maturitas* 2003;46 Suppl. 1:S31–7.

▶ Stegeman BH, de Bastos M, Rosendaal FR, *et al*. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* 2013;347:f5298.

▶ Roach EJR, Helmerhorst FM, Lijfering MW, *et al*. Combined oral contraceptives: the risk of myocardial infarction and ischaemic stroke. *Cochrane Database Syst Rev* 2018;(3) CD011054.

▶ Oedingen C, Scholz S, Razum O. Systematic review and meta-analysis of the association of combined oral contraceptives on the risk of venous thromboembolism: the role of the progestogen type and estrogen dose. *Thromb Res* 2018;165:68–78.

▶ Calhoun AH. Hormonal contraceptives and migraine with aura-is there still a risk? (Review) *Headache* 2017;57:184–93.

obese women, smokers, and to women with inherited thrombophilias.

However, valid clinical indications should not be underestimated or undertreated—so far there are no data suggesting that abnormal uterine bleeding due to ovulatory disorders could not be treated with NET in all patients. Nevertheless, the use of alternative progestogen therapies, especially that of the LNG-IUS must not be forgotten.

There is a need for future studies focusing on safety and the most appropriate use of different progestogens. The equivalent doses needed for endometrial transformation should be studied in more detail to optimise the progestogen regimens. In addition, the risk for thrombosis associated with therapeutic use of NET should be studied further. Considering the wide variety of indications for progestogen use across a woman's life cycle and the potential adverse events, the use and optimisation of progestogen therapies remains an important field of study.

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