

Positioning gestrinone among the progestins: a narrative review of pharmacology, efficacy, safety, and tolerability

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Structured abstract

Introduction. Gestrinone is an androgenic progestin derived from 19-nortestosterone, in use for four decades in endometriosis and other estrogen-dependent conditions. It has largely disappeared from contemporary progestin taxonomies and is sometimes described as an anabolic-androgenic steroid. This review examines its pharmacology and the evidence for its use.

Areas covered. Narrative review without a prespecified protocol, based on searches of PubMed, trial registries and regulatory sources, without date or language limits. It integrates chemistry and multireceptor pharmacology, pharmacokinetics, comparative efficacy against danazol, gonadotropin-releasing hormone (GnRH) agonists and other progestins, and safety, by indication, route and formulation.

Expert opinion. Gestrinone was active in every controlled setting tested, and the direct comparisons against danazol and a GnRH agonist detected no difference in the principal pain outcomes, in trials too small to establish equivalence; no direct comparison with dienogest exists. Its hallmark is an androgenic-metabolic signature, and its androgenic effects are not consistently milder than those of danazol. Skeletal findings varied between studies and doses and do not establish long-term protection or the absence of a need for add-back therapy. Priorities are formulation-specific exposure data and contemporary comparisons.

Article highlights

- Gestrinone is an ethynylated gonane of the 19-nortestosterone family, and what distinguishes it within the class is its antiprogestational component, the direction of its androgenic effect and its long duration of action, rather than its structural origin.
- Its central antigonadotropic action produces therapeutic amenorrhea with only moderate hypoestrogenism, to which a direct androgenic action and an antiprogestational one are added.
- Controlled trials document activity in endometriosis, leiomyoma, heavy uterine bleeding and mastalgia, at different levels of evidence; the direct comparisons against danazol and a gonadotropin-releasing hormone (GnRH) agonist detected no difference in the principal pain outcomes, with two additional findings favouring gestrinone, and none was designed to establish equivalence.

- Reported androgenic effects are not consistently milder than those of danazol, and skeletal findings varied between studies and doses, which does not establish long-term protection or that add-back therapy can be omitted.
- Anti-doping classification reflects androgenic activity and potential for misuse in sport; it does not quantify anabolic efficacy, for which we identified no published measurement.
- The priority gaps are formulation-specific pharmacokinetics, the absence of a direct comparison with dienogest, and longer-term skeletal, hepatic, metabolic and vascular data.

1. Introduction

Gestrinone (R-2323) is a synthetic androgenic progestin derived from 19-nortestosterone, with a multireceptor profile (antigonadotropic, antiprogesterational, androgenic and antiestrogenic actions) [1,2]. First investigated as a weekly oral contraceptive and later established as a therapy for estrogen-dependent disease, it has been used clinically for four decades.

After the contraceptive programme ended, its efficacy in endometriosis was described from the early 1980s and examined in randomized trials against danazol and a gonadotropin-releasing hormone (GnRH) agonist [3,4]. The oral 2.5-mg capsule is the presentation that has held marketing authorization; its availability differs between countries. Beyond the oral route, gestrinone has been studied as a compounded vaginal preparation [5], as a subcutaneous Silastic implant [6] and, more recently, as a subcutaneous pellet under investigation [7].

Gestrinone is also structurally related to tetrahydrogestrinone (THG), the designer steroid identified in the BALCO (Bay Area Laboratory Co-operative) doping investigation [8]. Structural relationship, receptor activity, anti-doping classification and demonstrated anabolic effect in humans are distinct questions, and section 8 examines each of them for what it does and does not settle about therapeutic use.

This review integrates the history, chemistry, pharmacology, pharmacokinetics, efficacy and safety of gestrinone, situating it among the androgenic progestins. It examines which therapeutic effects are documented, how its profile differs from that of the other agents of the class, and which studies would clarify its contemporary role.

1.1 Literature search and narrative synthesis

The original manuscript was developed as a narrative review without a prespecified systematic-review protocol. PubMed was searched without date or language filters, most recently in September 2026. One search combined the drug name with its synonyms and development codes (gestrinone, gestrinona, ethynorgestrienone, R-2323, Dimetriose, Dimetrose, Nemestran), using both the controlled vocabulary and title-abstract fields. The second combined endometriosis with named hormonal comparators (dienogest, norethisterone, medroxyprogesterone, levonorgestrel, etonogestrel, danazol, gestrinone, GnRH analogues) and with systematic-review or meta-analysis publication terms. Trial registries (ClinicalTrials.gov, ReBEC) and regulatory sources were consulted separately, and reference lists of the retrieved articles were screened. The complete Boolean strings are available from the authors on request.

Titles, relevant abstracts and accessible full texts were examined. Selection prioritized human efficacy, safety, exposure and formulation studies, comparative syntheses, and mechanistic evidence relevant to specific claims. Findings were interpreted by indication, regimen, comparator, outcome and time. Multiple reports and updated reviews were considered together to avoid treating overlapping evidence as independent confirmation.

Selection was purposive rather than exhaustive. No independent duplicate screening or new formal risk-of-bias or Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment was undertaken; certainty ratings belong to the cited reviews. Full-text access and interpretability could influence selection despite unrestricted search language. AI assistance was used as declared at the end of the manuscript; it did not constitute independent reviewer assessment.

2. History and development

Gestrinone was developed by Roussel-Uclaf, the company that would later develop mifepristone (RU-486), among potent progestins derived from 19-nortestosterone, and laboratory and clinical evaluation of the compound was already under way by 1966 [9]. It was investigated as a long-acting contraceptive by successive groups: as a weekly oral agent [9] and, in a multicentre implant programme coordinated by the Population Council, as a subdermal Silastic system releasing gestrinone at a near-zero-order rate of about 317 µg/day for more than a year [10]. In that programme, recruitment was interrupted after reports of raised transaminases at one centre and of androgenic effects at another, and development of the compound for contraception did not continue [10]. The oral experience pointed the same way, with intermenstrual bleeding and androgenic effects prominent among the reasons for discontinuation [9].

In 1982, Elsimar Coutinho reported the treatment of endometriosis with gestrinone, exploiting the pharmacology that had rendered it unviable as a contraceptive, central suppression with partial preservation of basal estrogen, which produced therapeutic amenorrhea without a menopausal state [11]. Over the following decade the indication extended to uterine leiomyoma and benign breast disease, with a controlled trial in cyclical mastalgia [12,13], and the oral, vaginal and subcutaneous routes were compared [6,14].

From the late 1980s, the evidence moved from single-group series to controlled comparison. Randomized trials detected no difference in the principal pain outcomes versus danazol [3,15,16] or versus the GnRH agonist leuprolide [4], in samples ranging from 39 to 269 women, and reported different profiles of adverse effects rather than a consistent advantage for either agent.

Two factual points close this history. The Silastic implants of the 1970s and the bioabsorbable pellet now under evaluation are separated by five decades and by different release characteristics, so experience with the former does not transfer to the latter [7]. And the clinical programmes that established its indications were conducted in gynaecology, in women with estrogen-dependent disease; no programme investigated it for anabolic purposes.

Its regulatory history has to be read product by product and country by country. In Brazil, the marketing authorizations for the two oral products were cancelled at the request of the authorization holders, for reasons of commercial interest and in view of the availability of therapeutic alternatives, and not as a regulatory action prompted by a safety concern [17]. In Australia, the authorization for the oral capsule was likewise cancelled at the sponsor's request, with effect from November 2016 [18]. An oral product remains listed in the catalogue of a Chinese manufacturer, with a current package insert [19], which identifies the product without certifying the present status of its registration. For the other markets in which gestrinone was once available, no primary regulatory act could be retrieved, and the reasons for withdrawal are therefore not established here.

3. Chemistry and pharmacology

3.1 Chemical structure and the multireceptor profile

Gestrinone (13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4,9,11-trien-3-one; synonyms ethynorgestrienone, R-2323, and RU-2323; CAS 16320-04-0; C₂₁H₂₄O₂; molar mass 308.42 g/mol) is derived from 19-nortestosterone and combines three structural features that define its pharmacology. The 19-nor nucleus (lacking the methyl at C-19) increases affinity for the progesterone receptor and carries the background androgenicity of the series. The 4,9,11-triene system with a 13 β -ethyl group confers great conformational mobility, and the 17 α -ethynyl group confers oral activity [1,2,20].

From this architecture follows the feature that most distinguishes it. Gestrinone is neither a "pure" agonist nor a "pure" antagonist of a single receptor but a multireceptor steroid that binds the progesterone (PR), androgen (AR), glucocorticoid (GR), and mineralocorticoid (MR) receptors but not the classical estrogen receptor (ER) [1]. The clinical effect results from the integration of a dominant central antigonadotropic action with a mixed peripheral profile (progestational/antiprogestational, androgenic, and indirect antiestrogenic).

3.2 Antigonadotropic action: the central, dominant mechanism

The antigonadotropic action is gestrinone's central mechanism, from which the other clinical properties derive, such as therapeutic amenorrhea, endometrial atrophy, and much of the antiestrogenic effect. The molecule suppresses the hypothalamic-pituitary-ovarian axis and abolishes the ovulatory luteinizing hormone (LH) surge, leading to anovulation, but it is an antigonadotropic of moderate intensity that lowers the gonadotropin surge without deeply suppressing basal levels and reduces estrogen only to an intermediate range, far from the hypoestrogenism of GnRH agonists [21].

In eumenorrheic women the LH surge fell by 59% and the follicle-stimulating hormone (FSH) surge by 37%, with a fall in preovulatory estradiol and blockade of ovulation in some cycles, and luteal progesterone fell from 21.25 to 7.25 ng/mL, a luteolytic property that, with the change in cervical mucus, makes up a dual contraceptive mechanism [21]. Two experiments show that the effect is central, not ovarian or local. In hypophysectomized rats stimulated by gonadotropins, gestrinone

did not reduce serum estradiol even at ten times the therapeutic dose (no reduction, 761.9 vs 714.3 pg/mL in controls, not significant) [22]. And, unlike danazol and testosterone, it does not inhibit the growth of human endometrial cells in vitro, so that the clinical atrophy reflects hormonal deprivation, not cytotoxicity [23].

The result is therapeutic amenorrhea with partial preservation of basal estrogen, which underpins the use in endometriosis and is the mechanism proposed for the skeletal findings.

3.3 Action at the progesterone receptor: why it is an antiprogestin

Gestrinone is historically described as an antiprogestin, having been "the first known antiprogestin to bind the progesterone receptor" [1]. The term, however, misleads, for it is not a pure antagonist like mifepristone but a partial agonist that binds the receptor with high affinity and activates it very little. In human uterine cytosol it showed the highest relative binding affinity (RBA 41.5) among 30 candidate antiprogestins (progesterone = 100 [2]). The complex, however, dissociates rapidly (affinity falling from 75 to 50 between 2 and 24 h), the opposite of full progestins, and in the Claiberg assay its curve is virtually flat, without stimulating endometrial proliferation [1], the signature of a weak progestin.

By occupying the receptor without triggering it, it competes with endogenous progesterone and produces a functionally antiprogesterational effect, documented in animal models [1]. Added to this is the fall in the hormone's availability, since suppression of the axis and blockade of ovulation lower luteal progesterone [21]. It is therefore better described as a steroid with functional antiprogesterational activity (competition with reduced activation, lower progesterone production, and endometrial atrophy) than as a receptor antagonist.

3.4 Androgenic action: direct and amplified by the fall in SHBG

Gestrinone's androgenicity has two mechanisms, one predominant. The main one is the direct androgenic action, for, as a 19-nortestosterone derivative, it binds and activates the androgen receptor, with activity comparable to that of norgestrel and norethisterone [1]. A neuronal model corroborates that the action is direct and non-aromatizable, since it amplifies excitotoxic death already at 0.1 nM, an effect abolished by flutamide and insensitive to aromatase inhibitors [24]. The androgenicity is therefore intrinsic, since gestrinone is not a prodrug and does not convert to testosterone or dihydrotestosterone.

The second mechanism amplifies the first. The fall in hepatic sex hormone-binding globulin (SHBG) production increases the unbound fraction of testosterone, although the absolute free concentration also depends on changes in total testosterone [25]. Hence a decisive clinical point, for many patients keep total testosterone normal or falling (suppression of LH and ovulation tends to reduce ovarian synthesis) but with a greater unbound fraction of testosterone, so that routine markers can mislead (the "androgenic paradox"). Thus effects such as acne, seborrhea, oily skin, hirsutism, altered libido and, at high or prolonged exposure, voice change or clitoral hypertrophy can occur even with normal total testosterone, through the sum of direct agonism, the increased free fraction, and individual tissue sensitivity.

3.5 Antiestrogenic action: indirect, without blocking the receptor

Gestrinone is clinically antiestrogenic but does not block the estrogen receptor, for in binding assays it and estradiol do not compete, and the molecule does not occupy the classical receptor [1,2]. The effect is indirect, by three routes. The main one is central and lowers ovarian estradiol by suppressing the axis rather than acting on the ovary directly, the basis of the moderate hypoestrogenic state [22]. The second is local: at clinical concentrations gestrinone non-competitively inhibits estradiol binding to type II nuclear sites [26] and dose-dependently reduces estrogen receptors in the target tissue, and consequently progesterone receptors [27]. The third is the androgenic predominance, which functionally antagonizes estrogen-dependent programs.

Two popular hypotheses do not hold: gestrinone is not a functional aromatase inhibitor and does not act consistently on 17 β -HSD [22], and the "masked" estrogenic component is demonstrable only in the rat, without agonist estrogenic activity in primates [28]. It is therefore more accurate to speak of functional hypoestrogenism, by central suppression, receptor reduction and androgenic antagonism, than of estrogen receptor antagonism.

3.6 Other pharmacological actions

Gestrinone has accessory effects of variable evidence. In vitro it is the most potent inhibitor of 3 β -hydroxysteroid dehydrogenase (3 β -HSD) in its series [29], with a net-zero effect on estrogen, since it raises 17 α -hydroxylase, 17,20-lyase, and aromatase in parallel, and the estradiol produced does not change [22], which reinforces that the antiestrogenic effect is central. It also binds the glucocorticoid receptor (and the mineralocorticoid) with notable affinity in vitro [1], of uncertain clinical relevance. In human cells it inhibits macrophage phagocytosis at a physiological concentration (63.5% versus 81.4% of phagocytic macrophages), without cytotoxicity [30], and in leiomyoma cells it inhibits proliferation through the ER α /c-Src/p38 MAPK pathway, cytostatically and without apoptosis at therapeutic concentrations [31].

A caution is warranted. Effects sometimes attributed to gestrinone (antiangiogenic via VEGF, antifibrotic via TGF- β , modulation of metalloproteinases) are described for the class but not established for gestrinone with direct evidence, and are therefore not asserted here.

Figure 1 summarizes this architecture, with a central, dominant antigonadotropic mechanism and an antiprogestational action that converge on the therapeutic effect, and a direct, isolated androgenic axis that accounts for the signature of side effects.

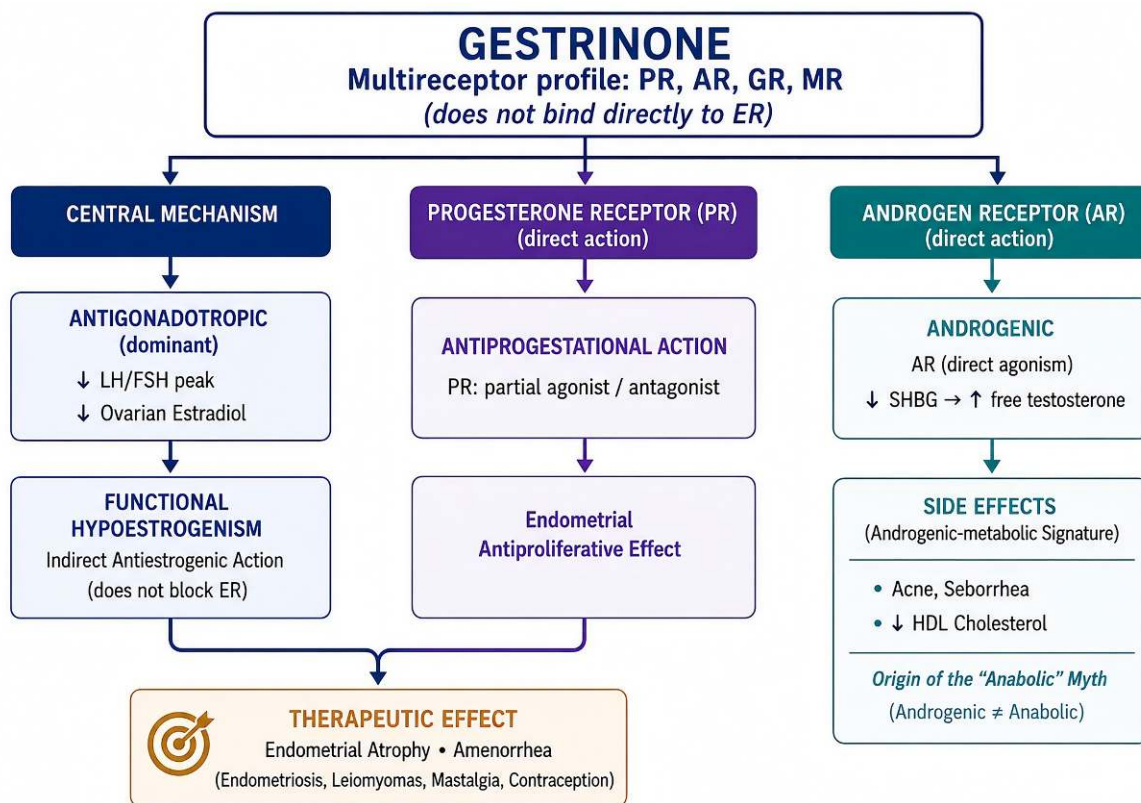


Figure 1. Pharmacological architecture of gestrinone. The central, dominant antigonadotropic mechanism, with the indirect antiestrogenic action that follows from it, and the antiprogestational action at the progesterone receptor converge on the therapeutic effect (endometrial atrophy, amenorrhea). Set apart, the androgenic actions, direct at the androgen receptor and indirect (increase in free testosterone), account for the androgenic-metabolic signature (acne, seborrhea, HDL fall).

4. Pharmacokinetics

4.1 Absorption, half-life, and plasma pharmacokinetics

Gestrinone is orally active, since the 17 α -ethynyl group protects it from first-pass metabolism, and its long duration of action allows a non-daily schedule, already present in the early studies, in which a weekly oral dose of 2.5 mg suppressed fertility [32]. In endometriosis, the standard regimen settled on 2.5 mg twice weekly. The serum half-life is reported as about 24 to 28 h [33] and the oral bioavailability at around 30% [34]. A half-life of this order would not, by itself, explain a twice-weekly regimen, and the clinical duration probably reflects the kinetics of effect in the target tissue, with a durable reduction of estrogen and progesterone receptors, rather than the drug's persistence in plasma [27]. Human concentration-time curves after oral and vaginal administration have been published [6], and a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay has been reported together with its application to a pharmacokinetic study [35]. Human pharmacokinetic information is therefore not absent. What is missing is exposure data detailed and

verifiable enough for each formulation in current use, particularly compounded preparations and pellets, and several of the quantitative estimates cited here still derive from secondary sources.

4.2 Metabolism and elimination

Gestrinone is cleared by hepatic biotransformation, chiefly hydroxylation, and the conjugates are excreted in urine and feces, with about 40 to 45% eliminated by the urinary route and 30 to 35% by the fecal route [7]. In urine after an oral dose, it and its metabolites are excreted almost entirely as glucuronide conjugates, with a hydroxylated metabolite recovered in greater amount than the parent drug [36]. In human hepatocytes, the main metabolite is 18-hydroxygestrinone conjugated to glucuronic acid at C-18, generated chiefly by CYP3A [20,37].

4.3 Routes, formulations, and systemic exposure

Being itself the active compound, gestrinone is effective at low, intermittent doses by the oral, vaginal and parenteral routes, but the route greatly alters systemic exposure. In the only primary comparison of serum levels, a 5-mg dose produced an oral peak of about 45 ng/mL around 5 h and a vaginal peak of only 9 ng/mL [6]. Despite that lower exposure, the vaginal route maintained efficacy on pain, with dose-dependent amenorrhea and less acne, seborrhea and weight gain than the oral route [14]; a preliminary report of a compounded vaginal preparation, in a non-indexed journal, is consistent with this pattern [5]. By the parenteral route, the classic Silastic implant released about 317 µg/day, a figure inferred from the drug residual in the capsule rather than from serum measurement [10]. The current formulation is an 85-mg bioabsorbable pellet, evaluated in the GLADE trial (NCT05570786), whose protocol specifies a pharmacokinetic substudy intended to provide, for the pellet, values of maximum concentration (C_{max}), area under the curve (AUC), time to maximum concentration (T_{max}) and terminal half-life [7]. The registry records the trial as completed, with a study completion date of 31 October 2025 and no results posted at the time of writing [38]. Two points bear on how the trial should be read. Participants received the pellet or placebo in addition to a levonorgestrel-releasing intrauterine system, so the design estimates the incremental effect of adding a pellet rather than the efficacy of gestrinone alone, and completion of a trial establishes neither efficacy nor marketing authorization.

5. Gestrinone among the androgenic progestins

5.1 The 19-nortestosterone family and gestrinone's place

The synthetic progestins fall into three structural groups: the progesterone derivatives, the spironolactone derivative (drospirenone) and the 19-nortestosterone family, which gathers nearly all the androgenic ones. This family divides into *estrane*s (13-methyl, such as norethisterone, lynestrenol, tibolone and dienogest) and *gonane*s (13-ethyl, such as levonorgestrel, gestodene and desogestrel). Dienogest is the atypical estrane of the series, the only non-ethynylated one, which underlies its antiandrogenic profile [39,40]. Two modifications govern the group. Removal of the C-19 methyl raises the affinity for the progesterone receptor by about an order of magnitude, and the 17α-ethynyl group shifts activity from the androgenic pole toward the progestational one and renders the molecule orally active [41].

Gestrinone is, unambiguously, a member of this family, an ethynylated gonane that shares with levonorgestrel the 13-ethyl skeleton and differs from it only in the 4,9,11-triene (Figure 2). Its receptor pharmacology was characterized in detail as early as the 1980s [1]. Even so, gestrinone is absent from the comparative tables and activity spectra of the main progestin reviews of the past two decades [39,40,41,42,43], probably because it is classed among the "formerly used progestins" [41]. Whether that classification is accurate depends on the jurisdiction.

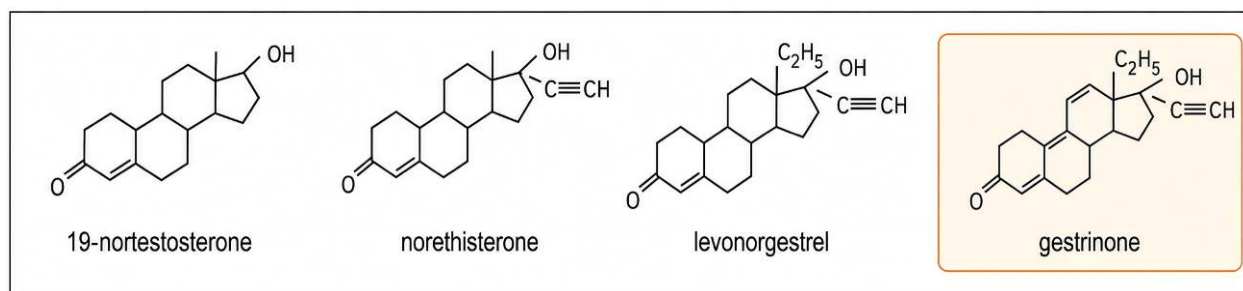


Figure 2. Gestrinone as an ordinary member of the 19-nortestosterone family. From the 19-nortestosterone skeleton (left), the androgenic progestins retain the 3-keto- Δ^4 ketone and the 17 β -hydroxyl and acquire the 17 α -ethynyl group (which confers oral activity). Norethisterone is the 13-methyl estrane, whereas levonorgestrel and gestrinone are 13-ethyl gonanes. Gestrinone differs only in the 9,11 system, which completes the 4,9,11-trien-3-one triene. Gestrinone's androgenicity is thus a trait shared with widely used progestins, not a singularity. (Authors' figure.)

5.2 The androgenicity gradient

Because the androgen and progesterone receptors are homologous, nearly every testosterone-derived progestin retains some androgenic affinity, and the molecules distribute along a continuous gradient [41,43]. On a single scale (metribolone = 100% at the androgen receptor), gestodene and levonorgestrel head the group, followed by norethisterone (moderate) and by desogestrel and norgestimate (low to minimal). At the opposite extreme is dienogest, frankly antiandrogenic [39,41]. The reviews summarize the same gradient by generation, from the second (levonorgestrel, the most androgenic) to the fourth (dienogest) [43,44].

Gestrinone occupies the strong end of this gradient, alongside levonorgestrel and tibolone [1,41], both of which are in routine gynaecological use. Its androgenicity is therefore a family trait rather than a singularity, although shared androgenicity does not make the agents of the class interchangeable.

A methodological caveat underpins the qualitative reading of Tables 1 and 2. The published relative binding affinities (RBAs) are not comparable across sources, because the standard set at 100% differs (metribolone/R1881 for norethisterone, levonorgestrel, and dienogest; testosterone for the only gestrinone data) [1,39,41]. Within a single source the numbers hold. Across sources, only the qualitative sign is comparable, and that is what the tables report.

Table 1. Qualitative activity spectrum of the 19-nortestosterone progestins (ordered by androgenicity)

Progestin	Progestational	Estrogenic	Antiestrogenic	Androgenic	Antiandrogenic	Glucocorticoid
<i>Tibolone</i>	±	+	+	++	–	–
Gestrinone †	±	–	+	++	–	+
Levonorgestrel	+	–	+	++	–	–
Norethisterone / NETA	+	+	+	+	–	–
Desogestrel / Etonogestrel	+	–	+	±	–	±
Dienogest	+	–	+	–	+	–

NETA, norethisterone acetate; PR, progesterone receptor. ++ strongly effective · + effective · ± weak or partial · – not effective or opposite. Gestrinone is a partial PR agonist and antiprogesterational (classified by the European Society of Human Reproduction and Embryology (ESHRE) as the only anti-progestogen among these agents) and binds the glucocorticoid receptor notably. Tibolone is not itself estrogenic; its estrogenic sign reflects its 3 α /3 β -hydroxy metabolites. †The gestrinone row is a qualitative inference: its binding data derive from a different reference standard (testosterone; [1,2]) than the other rows (metribolone/R1881; [39,40,41]), so its placement in the gradient is not a homologated measurement. Relative binding affinities are not comparable across sources, so only the qualitative sign is shown; see text.

5.3 The metabolic signature

Androgenicity translates into a concrete metabolic signature common to the whole class. The androgenic progestins raise hepatic lipase and oppose the estrogenic stimulus on liver proteins, with a fall in SHBG and high-density lipoprotein (HDL) and a rise in low-density lipoprotein (LDL) [40,41]. The intensity follows the gradient. Oral levonorgestrel lowers SHBG by about 50% [39]. Tibolone lowers SHBG, HDL, and triglycerides by around 50%, 30%, and 20% [41], and gestrinone occupies the most intense extreme, with SHBG practically collapsing, from about 55 to 7 nmol/L (a fall of 85 to 90%) within a few weeks [25,45], and HDL falling by 32 to 44% [46,47].

In the less androgenic progestins, the same signature appears attenuated, whether in norethisterone or in desogestrel and etonogestrel, whose androgenic affinity is about half that of levonorgestrel [40,41]. These are reversible changes and not peculiar to gestrinone, which merely occupies the strong end of a class effect. At the opposite pole is dienogest, which, from the same molecule but non-ethynylated, is antiandrogenic (30 to 40% of the potency of cyproterone acetate) and reverses the signature, for it does not bind SHBG and does not lower HDL; an increase of about 18% was reported in a comparison of estrogen-containing menopausal regimens, a result that should not be attributed to dienogest monotherapy [48].

Table 2. Androgenic-metabolic signature of the 19-nortestosterone progestins

Progestin	Typical dose · route	Androgenic AEs	SHBG	HDL
<i>Tibolone</i>	2.5 mg/day (menopause)	androgenic (via its Δ 4 metabolite)	↓↓	↓
Gestrinone	2.5 mg twice weekly, oral	acne, seborrhea	↓↓↓	↓↓
Levonorgestrel	oral (COC/POP); LNG-IUS 52 mg (local)	oral: strong; local IUS attenuates	↓↓	↓
Norethisterone / NETA	5 mg/day, oral	moderate	↓	↓
Desogestrel / Etonogestrel	POP; implant	low	↓ (mild)	neutral

Progestin	Typical dose · route	Androgenic AEs	SHBG	HDL
Dienogest	2 mg/day, oral	minimal; improves acne	no binding	↑‡

AEs, adverse events; COC, combined oral contraceptive; HDL, high-density lipoprotein; LNG-IUS, levonorgestrel-releasing intrauterine system; NETA, norethisterone acetate; POP, progestin-only pill; SHBG, sex hormone-binding globulin. Direction of effect: ↑ increase · ↓ decrease · ↓↓ and ↓↓↓ marked decrease; ‡the arrows denote changes in circulating concentrations, whereas "no binding" for dienogest denotes absence of affinity for SHBG. The HDL increase reported for dienogest (about 18%) comes from estrogen-containing menopausal regimens and should not be read as an effect of dienogest monotherapy. Compiled from [39,40,41,48]; the gestrinone row derives from [25,45,46,47].

5.4 Reinserting gestrinone into the class

Membership of the family, however, is the least informative thing that can be said about a molecule, and the differences within the class matter more than the shared origin. Three of them separate gestrinone from its congeners. The first is the antiprogesterone component, marked in gestrinone and absent in levonorgestrel and norethisterone, which brings it mechanistically closer to the progesterone receptor modulators and is the most plausible explanation for the reduction in leiomyoma volume, an effect the other androgenic progestins of the class do not produce. The second is the direction of the androgenic effect, which places gestrinone at one end of the gradient and dienogest, frankly antiandrogenic, at the other, with consequences for the cutaneous and metabolic profile that have not been matched by comparative efficacy data. The third is the long duration of action, which allows a twice-weekly rather than a daily regimen. Structural kinship does not by itself predict any of these, and it should not be read as evidence that agents of the same family behave alike in the clinic.

Placing it in the taxonomy from which it was omitted (Figure 3) is therefore a starting point rather than a conclusion: it identifies the agents against which gestrinone should be compared, and the sections that follow examine what the clinical evidence does and does not establish about that comparison.

Classification of Progestins

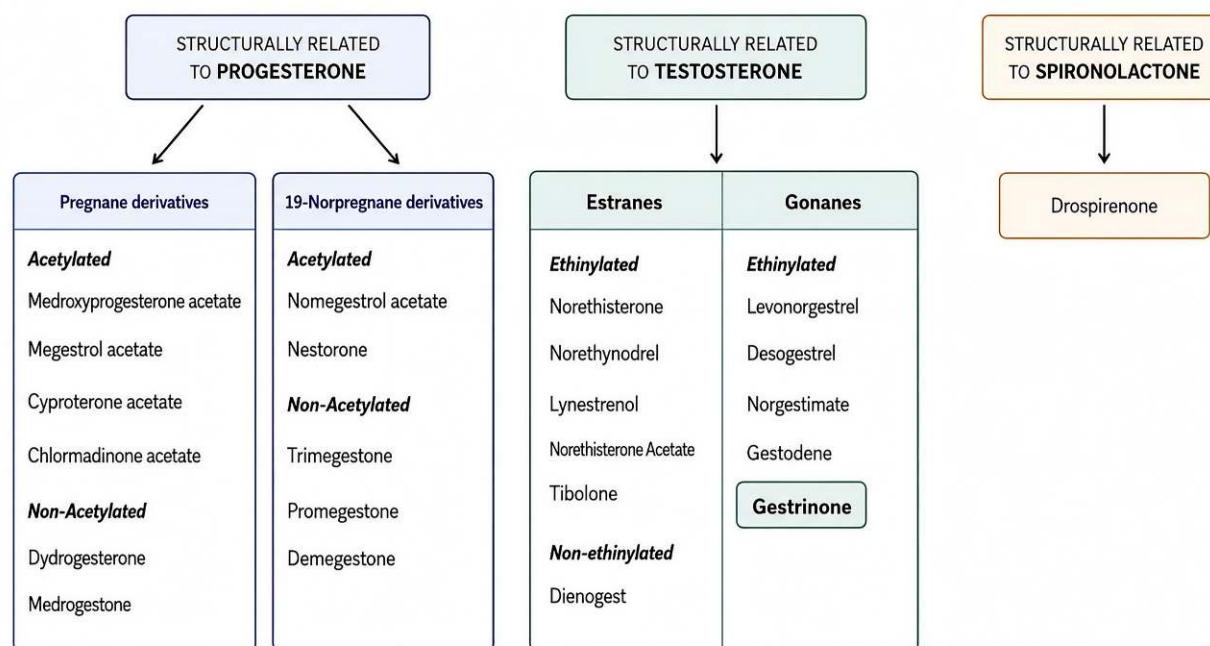


Figure 3. Classification of the progestins by structural origin (derived from progesterone, testosterone, or spironolactone), with gestrinone (highlighted) reinserted among the ethinylated gonanes. (Authors' figure.)

6. Efficacy in gynecological conditions

6.1 The contraceptive origin

The clinical path begins in contraception, and its figures explain the migration to therapeutic gynecology. As a weekly oral contraceptive (5 mg), suppression of the axis prevented pregnancy, but incompletely. In 28 women there were no pregnancies over 138 cycles, yet about 31% still ovulated; the authors cited failure rates of 7 to 9% reported for the method in other series of the period [9]. The critical point was cycle control. Intermenstrual bleeding affected 81% of users, and about one-third abandoned the method because of headache, weight gain, and acne [9], a decisive combination for a contraceptive of healthy women.

The subdermal implant told a similar story. In the comparative trial against levonorgestrel (100 women), gestrinone was at least as effective, with no pregnancies over 504 woman-months, but it was discontinued in the face of reports of hirsutism and raised transaminases [10]. Contraceptive development did not continue [9,10].

One late niche remained, emergency contraception, in which the mechanism is not to inhibit ovulation but to impair endometrial receptivity [49]; a double-blind trial of 998 women found gestrinone comparable to mifepristone (Table 3) [50]. What made the molecule unviable as a contraceptive is what came to define it in therapeutics: sustained central suppression and

antiprogestational action on the endometrium, undesirable in a healthy user, are what is sought in estrogen-dependent disease.

6.2 Endometriosis

Endometriosis is the established indication and the ground on which efficacy was best studied. In the first description, 20 women with laparoscopically confirmed disease were treated (5 mg twice weekly), and all became amenorrheic by the end of the second month, most asymptomatic by the third, and 66% of those wishing to conceive did so, with an intermittent regimen far lighter than the daily danazol then in use [11].

The only placebo-controlled trial, and the first of its kind for any endometriosis treatment, assessed laparoscopic appearance rather than symptoms. In 35 women with asymptomatic disease, the lesions progressed in 8 of 17 women on placebo and in none of the 18 assessed on gestrinone ($p = 0.002$), and improved in 15 of 18 versus 5 of 17 ($p = 0.004$) [51]. These are laparoscopic findings in a small sample of asymptomatic women observed over the treatment period. They show that the drug acts on the lesions themselves, and they do not establish a durable effect on the natural history of the disease, on recurrence after treatment, or on fertility.

Against active comparators the record is more detailed. In the first randomized trial against danazol, in 39 infertile women, no difference was detected in the revised American Fertility Society (r-AFS) score, in pain relief, in recurrence at 12 months or in pregnancy [3], and a histological substudy found similar endometrial atrophy at six months [52]. A larger multicentre comparison randomized 269 women to gestrinone (132) or danazol (137) and reported similar numbers of withdrawals for adverse symptoms, 15 and 17, with more hirsutism on gestrinone [16].

The most informative comparison was with a GnRH agonist. In a double-blind multicentre study, 55 women with moderate to severe pain were randomized to oral gestrinone or depot leuprolide acetate for six months, with six further months of follow-up, and pain relief at the end of treatment did not differ between the groups [4]. In the 17 women per group in whom recurrence was assessed, moderate to severe pain recurred in 52.9% after leuprolide and in 11.8% after gestrinone (odds ratio [OR] 0.12; $p = 0.03$), a difference derived from small numbers and therefore imprecise. Serial bone densitometry was completed in 41 of the 55 women, 19 and 22 per group: lumbar bone mineral density fell by about 3% with leuprolide, whereas with gestrinone it changed little, with a non-significant increase of 0.9% at six months and 2.1% at twelve. Hot flashes were less frequent with gestrinone (30% versus 68%). The same trial documented a fall in HDL cholesterol during gestrinone treatment.

The mechanism proposed for the skeletal findings is that, acting in an androgenic manner rather than through deep hypoestrogenism, gestrinone leaves estradiol in an intermediate range (50 to 65 pg/mL). A double-blind two-dose trial reduced the AFS score at both doses without significant change in estradiol or densitometry at six months [53]. In tissue, gestrinone lowers the estrogen and progesterone receptors in eutopic endometrium but not in endometriosis lesions, and the authors conclude that efficacy occurs through routes other than modulation of these receptors,

with emphasis on the androgenic action [54]. As a postsurgical adjuvant, it sustained its performance for at least four years [55].

All these direct comparisons were against danazol and the GnRH agonists, the standards of the 1980s and 1990s. No randomized trial has compared gestrinone with dienogest, today the reference progestin in endometriosis, and that is the most important gap to fill.

6.3 Fibroids and uterine bleeding

Outside endometriosis, the best-documented indication is uterine leiomyoma, almost all from a single Brazilian series, with two components of unequal magnitude. On bleeding, the effect is marked and reliable, and in a randomized cohort of 97 women bleeding ceased in about half by the second month and in 95% by the fourth, with amenorrhea in 92% of those still on treatment at 12 months and a rise in hemoglobin [56]. On volume, the reduction is real but moderate, and in continuous treatment for up to two years (100 women), the mean volume fell from 339 to 273 cm³ ($p = 0.010$), decreasing in about three-quarters of the patients [12]. Very large uteri responded with a doubled dose [57,58].

This volume reduction distinguishes gestrinone within the class. The common progestins control fibroid bleeding by endometrial action but do not reduce tumour volume [59,60], which is a property of the selective progesterone receptor modulators acting on the leiomyoma itself [60]. Gestrinone's antiprogesterone component brings it mechanistically closer to that group, with preclinical support in the inhibition of leiomyoma cell proliferation in vitro [31].

In increased uterine bleeding without fibroids, the only placebo-controlled trial, with objective measurement of loss, treated 19 women with menorrhagia, and gestrinone (2.5 mg twice weekly) reduced loss in 15 (79%), with amenorrhea in 5 by the fourth week and in 10 by the twelfth [61]. Notably, three of the four non-responders had unsuspected submucosal fibroids, a reminder that failure should prompt a search for intracavitary pathology. Reviews from the early 2000s placed gestrinone among the options for these indications and treated it as second-line, chiefly on grounds of cost [62,63].

A distinct surgical indication has also been studied. In preparation for hysteroscopy, gestrinone produced greater endometrial atrophy than danazol, with shorter operating time and greater patient satisfaction, on two weekly doses against three daily [64].

6.4 Mastalgia and benign breast disease

Gestrinone was also studied in cyclical breast pain, with the best level of evidence among the minor indications. In a double-blind, placebo-controlled multicenter trial (145 women), gestrinone (2.5 mg twice weekly for three months) reduced breast pain by about 80% versus 37% on placebo (visual analog scale 11.7 versus 36.7 at the third month; $p = 0.0001$), with disappearance of mastalgia in 22% versus 2% ($p = 0.0005$) and a good or excellent result in 89% versus 25% [13]. Adverse effects, chiefly androgenic, were more frequent with gestrinone (41% versus 14%) but mild and reversible, and there were fewer withdrawals than on placebo (4 of 73 versus 11 of 72).

An earlier open series in fibrocystic breast disease pointed in the same direction, at the cost of acne and seborrhea in about 70% [65]. Gestrinone is therefore active in cyclical mastalgia, although it is not a first-line option.

6.5 Comparative efficacy and its limitations

The pattern across the four indications is coherent. Gestrinone was active in every setting in which it was studied, and in the direct historical comparisons against danazol and a GnRH agonist no trial detected a difference in the principal pain outcomes during treatment, while two additional findings favoured gestrinone: lower recurrence after the comparison with leuprolide and better preoperative endometrial preparation than danazol. That is still a weaker statement than equivalence. The trials were small, most were conducted between 1985 and 1996, and none defined in advance a margin of equivalence or non-inferiority, so a difference of clinically relevant size cannot be excluded. Table 3 sets out the controlled comparisons.

The higher-level syntheses have to be read with the same care. The updated Cochrane review found that oral progestogens probably reduce overall pain and dysmenorrhoea compared with placebo, while the evidence comparing hormonal suppression strategies remains less certain [66]. The 2022 ESHRE guideline discusses the historical evidence of activity for gestrinone but no longer retains anti-progestogens among its treatment recommendations [67], a distinction that should be read as a judgment on the age and quality of the evidence rather than as a demonstration of lack of efficacy. The two network meta-analyses address different outcomes, with limited direct evidence for gestrinone in each. One places gestrinone behind dienogest and the levonorgestrel intrauterine system for recurrence after surgery [68], whereas the more recent, of 31 trials and 8,665 participants, gives it the highest surface under the cumulative ranking curve (SUCRA) for non-menstrual pelvic pain [69]. That result needs qualification on three counts: the network for that outcome comprised 13 trials, and gestrinone's direct contribution to it came from the 27 women of the gestrinone arm of the Italian trial; dienogest was not among the treatments included in that particular network, so the ranking does not establish superiority over it; and SUCRA summarizes ranking probability rather than the size of an effect.

Evidence that does not favour gestrinone belongs in the same balance. A meta-analysis of dydrogesterone in endometriosis included eight studies comparing it with gestrinone and reported less dysmenorrhoea at twelve months with dydrogesterone, with no clear difference at three and six months and none for pelvic pain, dyspareunia or recurrence, alongside fewer elevations of transaminases, less acne and less vaginal dryness; the authors judged the quantity and quality of that evidence to be very low [70]. Being active, in short, is not the same as being preferable, and the comparative evidence available does not settle the choice among the agents now in use.

Figure 4 summarizes the outcomes reported across these conditions.

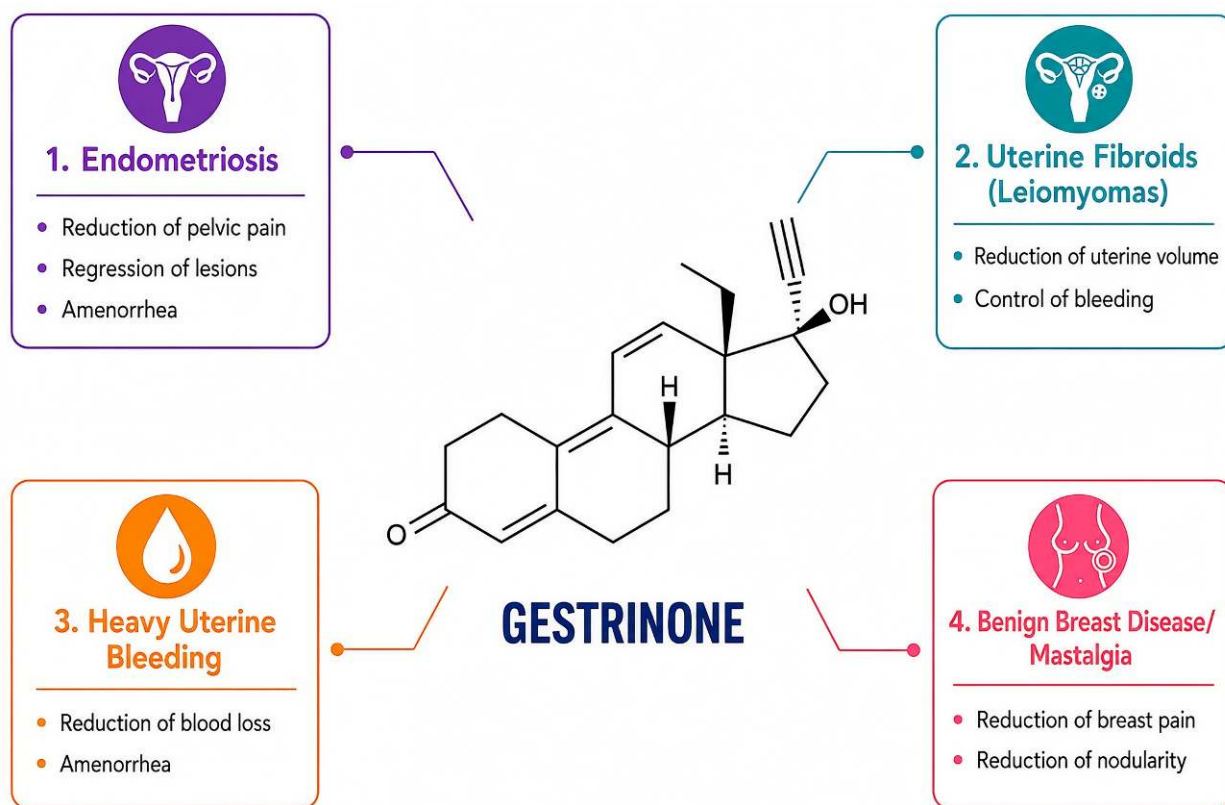


Figure 4. Outcomes reported for gestrinone in the main estrogen-dependent gynecological conditions. The strength of the underlying evidence differs across the four conditions, and the effects shown are those observed during treatment in the studies cited. (Authors' figure.)

Table 3. Comparative studies of gestrinone in gynaecological conditions

Comparator	Condition	Participants	Design and outcome assessed	Result	Ref.	Main limitation
Placebo	Endometriosis, asymptomatic	35	Double-blind randomized trial; laparoscopic appearance	Lesions progressed in 8/17 on placebo and 0/18 on gestrinone (p = 0.002)	[51]	Asymptomatic disease; small sample; no post-treatment outcome
Danazol	Endometriosis, infertile women	39	Randomized trial; r-AFS score, pain, pregnancy	No significant difference in any outcome assessed	[3]	Not powered for equivalence; only 16 accepted repeat laparoscopy
Danazol	Endometriosis	269	Multicentre randomized trial; symptoms and tolerability	Withdrawals for adverse symptoms 15 vs 17; more hirsutism with gestrinone	[16]	Full text not retrieved; possible multiple reports of one trial
Danazol	Endometriosis	164	Open randomized trial, 24 weeks; symptoms and tolerability	Symptomatic response in both arms; acne and irregular bleeding less frequent with danazol	[15]	Open label
Danazol	Endometriosis	27	Open comparative study; tissue and endocrine response	Androgenic events in 10/15 on gestrinone and 5/12 on danazol	[45]	Very small; open label

Comparator	Condition	Participants	Design and outcome assessed	Result	Ref.	Main limitation
Leuprolide (GnRH agonist)	Endometriosis, moderate to severe pain	55	Double-blind randomized trial; pain at 6 months, then 6 months' observation	No difference at 6 months; recurrence 11.8% vs 52.9% among 17 per group; lumbar bone density preserved vs -3%, assessed in 41 of 55	[4]	Small subgroups for recurrence and densitometry
Danazol	Preoperative preparation for hysteroscopic surgery	135 (68 vs 67)	Prospective randomized trial; endometrial atrophy, operating time, satisfaction	Greater atrophy, shorter operating time and greater satisfaction with gestrinone	[64]	Surgical preparation, not a treatment outcome
Gestrinone regimens (three doses and routes)	Uterine leiomyoma	97 (34, 36, 27)	Comparative study of regimens; bleeding control and uterine volume	Bleeding ceased in about 95% by month 4	[56]	No comparator outside gestrinone; single centre
Placebo	Heavy uterine bleeding	19	Sequential design: two placebo cycles followed by three treatment cycles in the same women; objective measurement of blood loss	Loss reduced in 15 of 19	[61]	Not a parallel randomized comparison; very small
Placebo	Cyclical mastalgia	145	Double-blind randomized trial; visual analogue pain score	11.7 vs 36.7 at month 3 (p = 0.0001)	[13]	Three months only; androgenic events 41% vs 14%
Mifepristone	Emergency contraception	998	Double-blind randomized trial; pregnancy rate	2.4% vs 1.8% (p = 0.51)	[50]	Different indication; not a chronic-use comparison

*GnRH, gonadotropin-releasing hormone; r-AFS, revised American Fertility Society score. The table lists the studies in which gestrinone was compared with placebo, with another drug, or between its own regimens, and is a selection rather than an exhaustive inventory; single-arm series are described in the text. *No randomized trial has compared gestrinone directly with dienogest*, which is the principal gap in the comparative evidence; the comparison with dienogest is available only indirectly, through network meta-analysis [68,69].*

7. Safety and tolerability

7.1 The general adverse-event profile

Comparative safety and tolerability require assessment of their own, and two recent syntheses describe the adverse-event profile of gestrinone with some precision. A meta-analysis of 16 studies and 1,286 women treated for endometriosis compared gestrinone with the other treatments, chiefly danazol; of the seven poolable events only two were significantly more frequent with gestrinone, acne (odds ratio [OR] 1.58; 95% confidence interval [CI] 1.06 to 2.36) and seborrhea (OR 3.11; 95% CI 1.95 to 4.93), both with moderate certainty, with no significant difference in bleeding, headache, hot flashes, nausea, or weight gain. Discontinuation attributable to adverse events was reported in four of the included studies, although the reviewers noted that the reasons were not described in sufficient detail to be pooled [34]. A systematic review dedicated to safety (32 studies, 3,745 women across all indications) reports the same pattern, with androgenic or expected events predominating. The proportions are not calculated over the whole population,

since each event was reported by a different subset of studies: acne and seborrhea in 111 of 260 women (42.7%), reduced libido in 61 of 230 (26.5%) and hoarseness in 31 of 887 (3.5%). The denominator should be read with the event [71]. Both caution that the base is limited and old, of low methodological quality, so that the estimates are indicative, not definitive.

7.2 The androgenic signature

The dominant axis is androgenic, as expected of a 19-nortestosterone derivative. Acne and seborrhea depend on dose and route, being less frequent by the vaginal route, and are followed by reduced libido, hirsutism and reduced breast volume. Weight gain of 0.9 to 8 kg was reported in a substantial proportion of treated women, which argues against the use of gestrinone as a slimming agent, as the authors of both syntheses themselves note [34,71]. Most effects regress on discontinuation, although the literature does not systematically characterize this reversibility. The exception is the voice, for the hoarseness reported in about 3.5% can be persistent and has no described reversal, being the effect that most warrants prior counseling. Whether the androgenic burden is lower than that of danazol is not settled by the available comparisons. The 39-woman trial recorded no hirsutism or voice change with gestrinone [3], but the larger open comparison of 164 women found acne and irregular bleeding less frequent with danazol [15], a smaller comparison reported androgenic events in 10 of 15 women on gestrinone against 5 of 12 on danazol [45], and the Cochrane synthesis found hirsutism more frequent with gestrinone (OR 2.63; 95% CI 1.60 to 4.32; two trials, 302 participants; very low certainty) [72]. The two drugs differ in the profile of androgenic effects rather than in a demonstrated advantage of one over the other.

7.3 The other side: what gestrinone does not do

By not inducing deep hypoestrogenism, it spares the menopausal state of the GnRH agonists, and in the trial against leuprolide hot flashes were less than half (30% versus 68%) [4]. Skeletal findings varied between studies and doses: in that same trial lumbar bone density was preserved over six months of treatment followed by six months of observation, whereas the agonist reduced it by about 3%; a two-dose trial found no significant change in densitometry at six months [53]; and a two-dose study of 11 women found changes that differed in direction between the two doses [73]. The safety review describes the bone data as limited and heterogeneous [71]. This is a relevant difference from the GnRH agonists, for which add-back therapy is standard, but it is not by itself evidence that add-back can be dispensed with over longer courses, since no study has followed bone density under gestrinone beyond one year. The hepatic data are also heterogeneous. The safety review recorded a rise in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and gamma-glutamyl transferase [GGT]) in 15.1% of patients, across four studies [71], whereas other trials observed no change [11,57]. On the metabolic plane, the androgenic signature (fall in SHBG and HDL) is reversible and is accompanied by a reduction in total cholesterol and triglycerides. The behavior of LDL is less consistent across studies, and the clinical significance of these changes in six-month treatments remains uncertain.

Two further gaps should be made explicit. There are no clinical data on venous thromboembolic risk. Because it does not induce an estrogen-dependent prothrombotic state, gestrinone would not

be expected to share the main risk mechanism of the estrogen-progestin agents, but this is a mechanistic expectation rather than an observation, and no assertion of vascular safety can be made. A registered observational study of endothelial function (NCT06402344) was ongoing at the time of writing and had posted no results [74]. Mood changes, described for several progestins, have not been systematically characterized for gestrinone.

7.4 Contraindications and use in pregnancy

Gestrinone should not be used in pregnancy, because of the risk of virilization of a female fetus. The product information for the oral formulation identifies pregnancy and breastfeeding as contraindications and calls for pregnancy to be excluded before treatment and for effective contraceptive precautions during it [19]; the regimens used in endometriosis should not be assumed to provide contraception themselves. The same document lists severe cardiac, hepatic or renal insufficiency, and a history of metabolic or vascular disorders during estrogen or progestin treatment, among its contraindications and precautions [19]. This product information applies to the oral formulation and does not establish the safety or the authorization of compounded vaginal preparations or pellets. Monitoring of transaminases before and during treatment remains advisable, consistent with the hepatic signal, and metabolism by CYP3A makes interactions clinically relevant, although label warnings about enzyme inducers should be distinguished from formal interaction studies, which have not been performed.

7.5 Interpreting the benefit-risk profile

At therapeutic doses and with monitoring, gestrinone was on the whole well tolerated in the studies reviewed, with an androgenic rather than hypoestrogenic profile, acne and seborrhea as the characteristic burden, and voice change as the effect that most warrants counselling before treatment. Against this stands the absence of a menopausal state, and the skeletal findings of the trial against a GnRH agonist. The balance is drawn from a small, aged and methodologically limited evidence base, the effects of higher doses and of the implant formulations are uncharacterized, and whether particular patients derive a better balance from gestrinone than from another agent of the class has not been tested prospectively. Tolerability and the expected profile of effects therefore remain part of a shared decision, alongside the uncertainty that surrounds comparative efficacy and long-term safety [75].

8. Between therapeutics and doping: the anabolic label of gestrinone

8.1 The BALCO case and tetrahydrogestrinone

The anabolic label is commonly traced to doping. Tetrahydrogestrinone (THG), a then-undetectable designer steroid, was identified in 2003 in the BALCO case, and the two names have been associated ever since [8,76].

THG was not a medicine but a designer steroid, a new chemical entity, unregistered and never tested in humans, synthesized to evade detection. Its kinship with gestrinone is structural and is in the name, but kinship is not identity. The conversion of one into the other is a laboratory reaction

that the human body does not perform, so that whoever receives gestrinone does not produce THG [37].

Gestrinone was never approved in the United States, unlike danazol. Why it came to be classified among prohibited anabolic agents is not documented in the sources reviewed here, and we do not attribute it to a single cause [71]. What can be said is that the absence of a United States market, together with the drug's association with doping, coincided with limited commercial interest and few modern studies.

8.2 Androgenicity, anabolism, and anti-doping status

Androgenicity and anabolic activity are distinct properties, expressed by the anabolic-to-androgenic ratio (the ratio between myotrophic and androgenic activity). Oxandrolone, the reference anabolic-androgenic steroid, has a ratio on the order of 10:1 relative to testosterone [77,78,79] and documented lean-mass gain in catabolic states, which supports its approved clinical use. The androgenic changes that gestrinone does produce, such as the fall in SHBG and the rise in free testosterone, likewise do not by themselves predict lean-mass gain or performance, so that its laboratory androgenicity does not equal anabolic efficacy. We did not identify a published anabolic-to-androgenic ratio for gestrinone in the sources reviewed, and none can be inferred from the available data.

Gestrinone appears on the World Anti-Doping Agency prohibited list among the anabolic androgenic steroids, in the same subcategory as tibolone, which is used at menopause and is not employed for anabolic or aesthetic purposes [80]. Inclusion on that list reflects a regulatory judgment about substances with androgenic activity and potential for misuse in sport. It is not a measurement of anabolic potency, and it is evidence neither for nor against a clinically meaningful anabolic effect. Neighboring progestins, such as norethisterone and levonorgestrel, remain in current gynecological use without this classification.

Outside its indications, gestrinone has been used with the promise of aesthetic and anabolic results, orally or by implant, an unapproved use. A small cross-sectional study of 30 women, in a non-indexed journal, recorded adverse effects in 63.3% of those who used it for this purpose, chiefly acne, hair loss, menstrual changes and clitoral enlargement, and yet 80% considered that it had been worth it [81]. Even the reference anabolics are not exempt in this population, and oxandrolone, the one with the lowest androgenicity, produces virilization in women at doses on the order of 10 mg a day [82].

9. Conclusion

Gestrinone is a 19-nortestosterone progestin with antigonadotropic, antiprogestational and androgenic actions. Controlled studies document activity in endometriosis, uterine leiomyoma, heavy uterine bleeding and cyclical mastalgia, at different levels of evidence. In the direct comparisons available, no difference in the principal pain outcomes was detected against danazol or a GnRH agonist, with two additional findings favouring gestrinone, in samples too small to establish equivalence, and no randomized trial has compared gestrinone with dienogest. Its

adverse-event profile is dominated by androgenic effects, which are not consistently milder than those of danazol; skeletal findings vary between studies and doses; and dedicated data on venous thromboembolism and drug interactions are lacking, while long-term safety remains insufficiently characterized. Marketing authorization for the oral product has been withdrawn in the countries for which a primary regulatory act could be retrieved, while preparations for the vaginal and subcutaneous routes are compounded or investigational.

10. Expert opinion

Gestrinone is a 19-nortestosterone progestin with documented clinical activity in several estrogen-dependent conditions and, above all, in endometriosis. The documented cancellations of oral-product authorizations in Brazil and Australia were requested by their holders; these administrative events do not by themselves establish clinical inefficacy. Its structural classification as a 19-nortestosterone progestin remains relevant regardless of commercial availability. What can be said about its place among the available treatments depends on evidence that is consistent in direction but limited in form, and the purpose of this section is to say where that evidence reaches and where it stops.

The trials that compared it with danazol and the GnRH agonists are, for the most part, from the 1980s and 1990s, and contemporary randomized controlled trials and pharmacokinetic data meeting current standards are lacking. Three gaps order the research agenda. The first is pharmacokinetic. Concentration-time data and a validated assay exist [6,35], so the question is not whether gestrinone has ever been measured in plasma, but whether exposure and its variability are characterized for the preparation actually in use. Oral, compounded vaginal and subcutaneous formulations should not inherit one another's claims about exposure, adherence or safety [7]. The second is comparative, for there is no direct randomized trial against dienogest, today the reference progestin in endometriosis, a question that requires an adequately designed contemporary comparative trial. The third is longitudinal, for the skeletal and lipid findings, heterogeneous and supported by small samples and short follow-up, call for prospective data spanning years, not months. As for the routes, the oral concentrates the greatest robustness of evidence and remains predominant, whereas the vaginal and the implant (the pioneering Silastic and the current bioabsorbable pellet) promise a lower serum peak and better adherence, hypotheses yet to be confirmed. Closing these gaps is the main pending task, and would allow gestrinone to be positioned with a precision that the current evidence does not yet permit.

Two things can nonetheless be said with reasonable confidence. Gestrinone was active in every controlled setting in which it was tested, and the direct historical comparisons against danazol and a GnRH agonist detected no difference in the principal pain outcomes they assessed, with two additional findings in its favour, namely recurrence after the leuprolide comparison and preoperative endometrial preparation against danazol. What cannot be said, on this evidence, is that it is equivalent to them, still less to the progestins that became standard afterwards, because the trials were small, old and not designed for that question. Where trials do not separate agents on efficacy, the expected profile of effects and individual tolerability necessarily enter a shared

decision, but they do so as one input among others and not as a substitute for the comparative data that are missing.

Whether any of this translates into a rule for selecting patients is precisely what has not been studied. Bone density, the androgenic burden on skin, and metabolic and vascular characteristics are plausible modifiers of the benefit-risk balance and the obvious candidates for a prospective comparison. None of them has been tested as such: no trial has randomized women by phenotype, and no analysis has shown that a given characteristic predicts a better outcome with gestrinone than with another agent of the class. To present them as prescribing criteria would go well beyond the evidence. They are stated here as research questions, and any use of gestrinone remains a shared decision informed by the individual clinical picture, by previous experience of adverse effects, and by what is regulatorily available in each country.

It is worth stating plainly what would be required for gestrinone to move beyond its current position. A contemporary development programme would have to characterize plasma exposure for the formulation actually in use, which has not been done to current standards; to demonstrate a clinically relevant advantage over agents that are already licensed, tolerated and inexpensive; and to address three points for which dedicated data would be expected, namely the hepatic signal, the risk of virilization of a female fetus in a drug that is not itself a reliable contraceptive, and a bleeding pattern that is a common reason for discontinuing hormonal treatment in endometriosis and leiomyoma. Whether that investment is undertaken will depend on how large the expected benefit proves to be. What does not depend on new development is the accuracy with which the drug is described where it is still prescribed, and that is the contribution intended here.

There remains the point that motivated much of its poor reputation. The use of gestrinone for aesthetic or anabolic purposes finds no support in studies and represents a deviation from its function, which should be countered and avoided. To distinguish clearly the therapeutic drug from this use, and from the stigma inherited from doping, is a condition for the molecule to be judged for what it in fact is, an agent with gynecological indications documented in controlled trials and a known profile of effects.

One conclusion follows from the material reviewed here rather than preceding it. Gestrinone is androgenic to a degree shared by progestins in current use; it is prohibited in sport, as other androgenic steroids are; and it has no demonstrated anabolic efficacy, no published anabolic-to-androgenic ratio and no controlled study of muscle mass or performance. These three statements are compatible with one another, and treating the third as though it followed from the first two is where the discussion of this molecule has most often gone wrong. Its omission from contemporary taxonomies of the progestins is not justified by its pharmacology, and putting it back among the 19-nortestosterone derivatives is less a rehabilitation than a course correction. Where it should sit among the agents in current use is a separate question, and one that contemporary comparative data would answer.

Five years from now, we expect the position of gestrinone to have been settled by data rather than by argument, and in one of two directions. If the pellet programme is published with interpretable exposure data and its randomized comparison is read for what it tests, the drug may acquire a

defined niche in women for whom a non-daily, non-hypoestrogenic regimen matters, and the case for a contemporary trial against dienogest will either be made or abandoned. If those data do not appear, gestrinone will remain what it is today, an agent with genuine historical evidence, no contemporary comparison, and a shrinking regulatory footprint, prescribed in a small number of countries and increasingly compounded outside them. Which of the two prevails will be decided by whether those data appear. In either case, the question that matters most for practice is whether the women who receive it, in whatever formulation, are told accurately what is and is not known about it.

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Author contributions

L Jacobsen is the sole author of this manuscript and was responsible for its conception, the literature search and analysis, and the writing and critical revision of the work.

Data availability statement

No new data were created or analyzed in this review; data sharing is not applicable.

Declaration of AI-assisted technologies

In preparing this manuscript, the author used the large language model Claude (Anthropic, Claude Opus 4.8) to assist with translation from Portuguese into English, language editing, and reference formatting, and used ChatGPT (OpenAI, GPT-5.5) to generate the schematic conceptual figures (Figures 1–4). These figures are conceptual illustrations and flow diagrams and do not depict research data or clinical images. All AI-assisted output was reviewed, verified, and edited by the author, who takes full responsibility for the content, accuracy, interpretation, and conclusions of this manuscript. No AI tool is listed as an author.

Abbreviations

3 β -HSD, 3 β -hydroxysteroid dehydrogenase; 17 β -HSD, 17 β -hydroxysteroid dehydrogenase; AEs, adverse events; AFS, American Fertility Society score (r-AFS, revised); ALT, alanine aminotransferase; AR, androgen receptor; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; BALCO, Bay Area Laboratory Co-operative; CAS, Chemical Abstracts Service registry; CI, confidence interval; C_{max}, maximum plasma concentration; COC, combined oral contraceptive; c-Src, cellular Src tyrosine-protein kinase; CYP3A, cytochrome P450 3A; ER, estrogen receptor (ER α , alpha subtype); ESHRE, European Society of Human Reproduction and Embryology; FIGO, International Federation of Gynecology and Obstetrics; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; HDL, high-density lipoprotein; IUD, intrauterine device; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LDL, low-density lipoprotein; LH, luteinizing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; MAPK, mitogen-activated protein kinase (p38 isoform); MR, mineralocorticoid receptor; NETA, norethisterone acetate; OR, odds ratio; POP, progestin-only pill; PR, progesterone receptor; R-2323, gestrinone development code (Roussel-Uclaf); RBA, relative binding affinity; SHBG, sex hormone-binding globulin; T₄, thyroxine; TGF- β , transforming growth factor- β ; THG, tetrahydrogestrinone; T_{max}, time to maximum concentration; VEGF, vascular endothelial growth factor.

Figure and table legends

Figure 1. Pharmacological architecture of gestrinone. The central, dominant antigonadotropic mechanism, with the indirect antiestrogenic action that follows from it, and the antiprogestational action at the progesterone receptor converge on the therapeutic effect (endometrial atrophy, amenorrhea). Set apart, the androgenic actions, direct at the androgen receptor and indirect (increase in free testosterone), account for the androgenic-metabolic signature (acne, seborrhea, HDL fall).

Figure 2. Gestrinone as an ordinary member of the 19-nortestosterone family. From the 19-nortestosterone skeleton (left), the androgenic progestins retain the 3-keto- Δ^4 ketone and the 17 β -hydroxyl and acquire the 17 α -ethynyl group (which confers oral activity). Norethisterone is the 13-methyl estrane, whereas levonorgestrel and gestrinone are 13-ethyl gonanes. Gestrinone differs only in the 9,11 system, which completes the 4,9,11-trien-3-one triene. Gestrinone's androgenicity is thus a trait shared with widely used progestins, not a singularity. (Authors' figure.)

Figure 3. Classification of the progestins by structural origin (derived from progesterone, testosterone, or spironolactone), with gestrinone (highlighted) reinserted among the ethynylated gonanes. (Authors' figure.)

Figure 4. Outcomes reported for gestrinone in the main estrogen-dependent gynecological conditions. The strength of the underlying evidence differs across the four conditions, and the effects shown are those observed during treatment in the studies cited. (Authors' figure.)

Table 1. Qualitative activity spectrum of the 19-nortestosterone progestins (ordered by androgenicity)

Table 2. Androgenic-metabolic signature of the 19-nortestosterone progestins

Table 3. Comparative studies of gestrinone in gynaecological conditions

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