Seventy-Five Microgram Desogestrel Minipill, A New Perspective in Estrogen-Free Contraception

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ABSTRACT: Progestin-only minipills have been available for over three decades, yet their use has been limited, because of a documented lower efficacy when compared to pills that combine estrogen and progestin. The availability of a new low-dose progestin-only minipill containing 75 μg desogestrel (DSG) offers a new perspective, since, in a large multicenter study, this minipill gave a crude Pearl index of 0.41 and an adjusted one of 0.14, which is comparable to indicies found in clinical trials of oral contraceptives. This minipill also allows for a 12-hour tolerance time in taking the pill. The high effectiveness of the DSG minipill is attributable to an almost constant inhibition of ovulation, as shown by the absence of elevated progesterone circulating levels and inhibition of follicular growth in the vast majority of cycles studied. Since irregular bleeding patterns are observed with all minipills, patterns experienced with DSG 75 μg have been compared to those obtained with levonogestrel 30 μg. As expected, the more pronounced ovarian inhibition produced wider bleeding variability with DSG, but also less bleeding overall. The DSG minipill is suitable for lactating women and represents a valuable addition to oral contraception.

KEYWORDS: oral contraception; minipill; desogestrel

HISTORICAL PERSPECTIVES

The contraceptive potential of synthetic, orally active progestins was first identified in the 1950s, utilizing the newly synthesized norethynodrel (NEL), which was administered daily during 20 days, followed by a break that produced a withdrawal bleeding.[1] However, careful chemical analysis of the commercial-grade compound utilized in clinical trials indicated that it was contaminated with as much as 4–7% of the estrogen mestranol (ME). Oddly, when additional purification reduced the estrogen content, rates of breakthrough bleeding increased forcing investigators to revert to the concept of using a "partially contaminated" progestin; it was then decided to add 1.5% ME to the purified NEL. The finding that an estrogen–progestin combination allowed better cycle control was responsible for the eventual utilization of an

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estrogen and a progestin in the formulation of oral contraceptives (OCs).[2] The combination tested by Gregory Pincus and his group, containing 9850 μg of NEL plus 150 μg of ME, was immediately patented by the Searle Company as *Enovid-10* and approved in 1960 by the U.S. Food and Drug Administration (FDA) as a contraceptive agent: thus, "the Pill" was officially born. One can easily agree with Malcolm Potts[3] that "the invention of the Pill was the greatest revolution that has ever occurred, or will ever occur, in family planning," since—for the first time—it separated sex and reproduction, while being virtually 100% effective and totally reversible.[4]

It should not be a surprise that a normal clinical titration of the "minimal effective oral dose" was not carried out in the initial days, when we consider that synthetic steroids, when administered orally, are less effective in rodents (the species utilized for bioassays) than in humans. Thus, extrapolation from animal dosage led to human overdosing.

Since the very first preparation introduced by Gregory Pincus, OC's effectiveness has never been questioned, and combined oral contraceptives soon became, and still are, by far the most popular method of reversible fertility control in the world. As OC's use increased and time passed, epidemiological evidence showed that the estrogen component of the pill is connected, in a dose-dependent way, with a series of rare adverse events, the first of which was the demonstration of an increased risk of venous thromboembolism[5] and, even if episodic and limited to women with other cardiovascular risk factors (such as smoke and hypertension), with myocardial infarction and stroke.[6]

While the estrogen content of combined oral contraceptives (COCs) has steadily declined over the years, its acceptability can still be seriously affected by these adverse events and, in certain cases, can even discourage use of the pill. Also minor adverse events, such as nausea, headache, and breast tenderness, traditionally referred to as being estrogen-dependent, may negatively affect a woman's perception of the method and induce her to discontinue using it. For this reason, investigations on ways to utilize progestins as the sole hormone for contraceptive purposes were never discontinued. In particular, clinical testing focused on the use of orally active progestins administered at low doses and without interruption.[7] This led to the creation of the so-called minipill. The first such preparation contained norethisterone (NET) at a daily dose of 350 μg and was approved for contraceptive purposes in 1973; the second utilized 75 μg of DL–norgestrel and was approved in 1974.[8]

So far, progestin-only pills (POPs) have not become a valid alternative to COCs, because current preparations do not consistently suppress ovulation; for this reason, their use effectiveness is considered more problematic than that of OCs. In this connection, it is a fact that ovarian response to POPs varies widely among individuals; Landgren and Diczfalusy[9] have reported that, in a number of studies evaluating the use of daily NET (300 μg), the percentage of cycles in which ovulation occurred ranged from 14% to 84%. In their fundamental study they have identified four distinct types of ovarian response to the NET-containing minipill: *type A*, with no sign of follicular or luteal activity, as evidenced by low estradiol and progesterone levels; *type B*, with marked cyclic follicular activity but no luteal function; *type C*, with normal follicular activity but reduced (insufficient) luteal activity; and *type D*, with estradiol and progesterone profiles indistinguishable from those of normally ovulating women. Not surprisingly, the current package labeling for POPs states that "the primary mechanism through which [brand-name] prevents conception is not known, but

progestogen-only oral contraceptives are known to alter the cervical mucus, exert a progestational effect on the endometrium, interfere with implantation, and in some patients, suppress ovulation."[8]

Several studies that have looked at the contraceptive effectiveness of progestin-only pills suggest that, in general, pregnancy rates are slightly higher in those who used it than for those who used COCs, especially among heavier women. In clinical practice, however, unwanted pregnancies are more often due to user than to method failure, with women not taking pills exactly on schedule at higher risk.

Several studies have also demonstrated that POPs have variable effects on the endometrium, resulting in an unpredictable bleeding pattern. Frequent and irregular bleeding are common, while bleeding episodes of long duration and amenorrhea are less likely to occur.

Finally, currently used progestins (i.e., NET and LNG) are first- and second-generation compounds, possessing dose-related androgenic effects.[10]

LOW-DOSE ORAL DESOGESTREL: PHARMACOKINETICS AND PHARMACODYNAMICS

Desogestrel (DSG) is a third-generation, high selective progestin with low androgenic properties; after oral administration, it is rapidly absorbed and converted, mainly in the liver, but possibly also in the intestinal wall, into its active metabolite, 3-keto DSG or etonogestrel.[11]

During multiple oral administration of Cerazette, the minipill containing 75-μg of DSG, peak serum concentration of etonogestrel of approximately 640 pg/mL are achieved within 2 hours, while a steady state is reached after 4 days.[12] When circulating, etonogestrel is largely bound to serum albumin (58%) and SHBG (38%), with only 3.5% remaining unbound and bioactive.[13] Etonogestrel is subsequently metabolized to polar derivatives in the liver, with an elimination half-life of about 30 hours. Enterohepatic circulation does not seem to contribute to the progestogenic effect of DSG.

In vitro receptor-binding studies have shown that etonogestrel possesses a higher affinity for progesterone receptors than LNG or NET, and a lower affinity for androgen receptors than LNG or gestodene (GSD); in addition, its binding to the estrogen receptor is negligible.[14] This pharmacological profile determines a higher selectivity index (which is the ratio of progesterone to androgen receptor-binding affinity) when compared to other contraceptive progestins (40 for etonogestrel, 26 for GSD, 8.8 for LNG, and 5.0 for NET).[14] In other words, etonogestrel is substantially devoid of adverse androgenic effects at the doses required to inhibit ovulation.

Dose-finding studies have clearly demonstrated that the daily administration of 60-μg DSG consistently inhibits ovulation in all women treated.[15,16] The ovulation-inhibiting dose of DSG was further investigated in a randomized, double-blind comparative study conducted over a 6-month period on 44 volunteers, in which the levels of ovarian suppression of DSG administered at the daily dose of 30, 50, or 75 μg were compared; the highest-dose preparation showed satisfactory suppression of ovarian function, with consistent inhibition of ovulation: serum progesterone concentrations never exceeded levels of 10 nmol/L,[17] as shown in FIGURE 1.

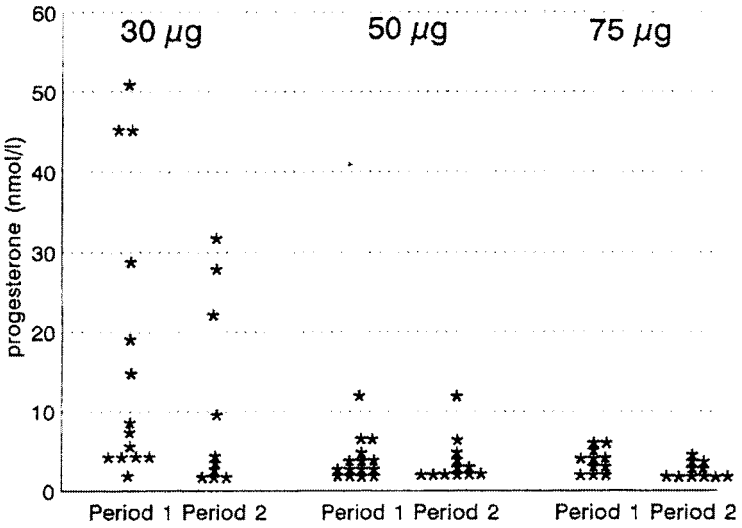

FIGURE 1. Maximum progesterone concentrations per subject per assessment period by dosage group. (From Rice *et al.*[15] Reproduced by permission.)

TABLE 1. Maximum progesterone concentrations per treatment group and treatment period

	Desogestrel treatment period		Levonorgestrel treatment period	
	7 *n* = 30	12 *n* = 29	7 *n* = 29	12 *n* = 28
<10 nmol (%)	29 (97)	28 (97)	10 (34)	14 (5)
10–30 nmol (%)	1 (3)	0	8 (28)	3 (11)
>30 nmol (%)	0[a] (0)	1 (3)[a]	11 (38)	11 (39)

SOURCE: Rice *et al.*[18]
[a]Denotes statistical significance ($P < .001$).

In another randomized, double-blind comparative study conducted to compare two progestin-only oral contraceptives containing either 75 µg of DSG or 30 µg of LNG, Rice *et al*. found that Cerazette inhibited ovulation in 58 out of the 59 cycles studied, while, in the LNG group, 16 out of the 57 cycles studied were shown to be ovulatory[18] (see TABLE 1). It is noteworthy that in this study ovulation was defined as follicular rupture on ultrasound scanning, followed by a rise in serum progesterone values.

A higher suppression of ovarian function in women treated with the DSG minipill when compared to women treated with LNG also can be inferred both from significantly lower estradiol serum concentrations and from the number of follicles exceed-

TABLE 2. Maximum and mean estradiol concentration per treatment group and treatment period

	Desogestrel		Levonorgestrel	
	Maximum (pmol/L)	Mean (pmol/L)	Maximum (pmol/L)	Mean (pmol/L)
Screening (cycle days 10–16)	1375	675	1310	653
Treatment period 7	615[a]	333	1230[a]	505[b]
Treatment period 12	487[c]	272	1420[c]	539[d]

SOURCE: Rice *et al.*[18]
[a]$P = .049$.
[b]$P = .001$.
[c]$P = .044$.
[d]$P = .003$.

TABLE 3. Follicular development per treatment group and treatment period

	Desogestrel treatment period		Levonogestrel treatment period	
	7 $n = 30$	12 $n = 29$	7 $n = 29$	12 $n = 28$
No follicular activity (%)	5 (17)	9 (31)	5 (17)	3 (11)
Persistent follicle (%)(15–30 mm)	17 (57)	15 (52)	10 (35)	8 (28)
Cyst > 30 mm (%)	6 (20)	4 (14)	5 (17)	7 (25)
Follcular rupture (%)	2 (6)	1 (3)	9 (31)	10 (36)

SOURCE: Rice *et al.*[18]

ing 30 mm in diameter, in spite of similar FSH suppression,[18,19] as shown in TABLES 2 and 3.

As to the effects of Cerazette on endometrium, 30% of women under 75 μg DSG daily had inactive or weakly proliferative endometria, while a secretory pattern was found in 40–50% of the women.[19] Secretory endometria were found in a higher percentage (70–85) of women under 30 μg LNG per day.

USE-EFFECTIVENESS

A large multicenter phase III study was conducted over a period of 12 months to compare the contraceptive efficacy of Cerazette and 30 μg LNG per day;[20] the study was conducted in a double-blind, randomized, group-comparative fashion and a total of 1320 women were enrolled. Approximately 30% of the subjects enrolled in each group were breast-feeding at the time the study started. Overall, seven pregnancies were reported during the study: three in the DSG group and four in the LNG group, giving a Pearl index of 0.41 and 1.55, respectively. When taking pregnancies attributable to gross noncompliance with the protocol (two in the DSG group and four in the LNG group) into account, only four pregnancies remain, one with the DSG

minipill and three with the LNG medication, which results in adjusted Pearl indices of 0.14 and 1.17, respectively. The differences in Pearl indices between DSG and LNG found in the study were not statistically significant, but a trend toward a better contraceptive efficacy for desogestrel was well documented.

Traditional POPs are associated with higher pregnancy rates than combined oral contraceptives, with a one-year pregnancy rate ranging from 0.5% for method failure to 5% in practical use.[8] The more pronounced suppression of the hypothalamic–pituitary–ovarian (HPO) axis and the consistent inhibition of ovulation well explain the better Pearl index for DSG, which is close to that reported for COCs.

For traditional progestin-only pills, compliance with the timing of doses has a major impact on contraceptive use-effectiveness. Although Cerazette should be taken at regular 24-hour intervals, a tolerance of 12 hours for missed tablets is allowed, since restoration of the fully suppressed HPO axis takes as long as low-dose combined formulations.

BLEEDING PATTERNS AND SUBJECTIVE ADVERSE EVENTS

It is generally accepted that combined oral contraceptives, taken for 21-day periods, with a 7-day pill-free interval in between, possess a regular, highly predictable bleeding pattern, as a consequence of the hormone withdrawal triggering endometrial shedding. On the other hand, progestins alone for contraceptive purposes do not allow any hormone withdrawal, thus giving rise to unpredictable bleeding patterns that negatively affect both acceptability and compliance by the women, and, eventually, the diffusion of the method. Not surprisingly, changes in menstrual patterns, including short cycles, amenorrhea, and spotting or breakthrough bleeding, are the major disadvantages of POPs.

To properly compare bleeding patterns of different contraceptive methods, the World Health Organization (WHO) recently recommended the use of the "reference period" analysis;[21] a 90-day reference period is generally used, since it seems to be long enough to properly characterize the bleeding pattern, without masking changes over time. Belsey and WHO,[22] using this methodological approach, compared the effects of various hormonal contraceptives. Frequent bleeding (more than five bleeding or spotting episodes in the reference period), infrequent bleeding (less than three bleeding episodes), and prolonged bleeding (one or more bleeding/spotting episodes lasting 14 days or more) were more common among POP than COC users, while no women had amenorrhea for any of the 90-day reference period; finally, two-thirds of POP users had none of the bleeding disturbances just mentioned, compared to about 90% of women under combined oral contraceptives.

The Collaborative Study Group on the Desogestrel-Containing Progestogen-only Pill[20] compared the bleeding patterns of two POPs containing 75 μg DSG and 30 μg LNG. To avoid artifacts induced by differences in initiating treatments among starters (women who were starting the POP for the first time), switchers (women who were switching from another oral contraceptive formulation), and breast-feeding women, the first reference period was taken as commencing 28 days after the first day of treatment ("shifted reference period"). In comparison to LNG, the bleeding pattern with DSG showed a larger variability, but less bleeding in terms of bleeding/spotting days and episodes, and the contribution of bleeding days (as opposed to

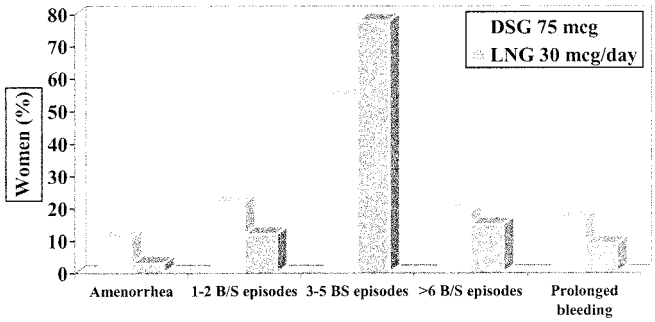

FIGURE 2. Time trend in the bleeding pattern parameters from the shifted reference period 1 to reference period 4 for (**a**) desogestrel and (**b**) levonorgestrel. (From Collaborative Study Group on the Desogestrel-Containing Progestogen-only Pill.[20] Reproduced by permission.)

spotting-only days) to this parameter was significantly smaller in the DSG group. This behavior can be attributed to the more pronounced ovarian inhibition and the more consistent block of ovulation. A shift in time toward more amenorrhea and infrequent bleeding was observed in the DSG group but not in the LNG one; in fact, during reference period 4, about 50% of women experienced amenorrhea or infrequent bleeding with DSG, compared to some 10% with LNG. Finally, in the DSG group, 80–90% of the women in reference period 4 had the same bleeding pattern or a pattern associated with less bleeding as compared to the bleeding pattern at the beginning of the treatment, as shown in FIGURE 2.

Overall, 22% of DSG users discontinued the method because of changes in bleeding pattern, compared to 18% of LNG users; this difference was not statistically significant.

According to the already quoted large, multicenter study,[20] the percentages of women with adverse and serious adverse experiences were comparable for DSG

TABLE 4. Frequently occurring adverse experiences among DSG and LNG POP users

	Number of women reporting adverse events	
Adverse event	Desogestrel 75 μg/day	Levonorgestrel 30 μg/day
Headache	89 (6.8%0	28 (5.9%)
Acne	54 (4.1%)	20 (3.2%)
Breast pain	49 (3.7%)	17 (3.6%)
Nausea	43 (3.3%)	8 (1.7%)
Vaginitis	42 (3.2%)	13 (2.7%)
Dysmenorrhea	18 (1.4%)	15 (3.2%)

SOURCE: Collaborative Study Group of the Desogestrel-Containing Progestogen-only Pill.[20]

(41.8% and 1.4%, respectively) and LNG (41.3% and 1.8%, respectively). Four serious adverse experiences (0.3%), all including an ovarian cyst, were reported as possibly related to the DSG use; two serious adverse experiences possibly related to LNG (one ovarian cyst and one ectopic pregnancy) occurred. Adverse experience occurring in more than 3% of women in any group are reported in TABLE 4. Finally, no significant effect in terms of changes in body weight was observed in either group.[20]

METABOLIC EFFECTS

The effect of the DSG-containing POP on various parameters of lipid metabolism was compared to that induced by the LNG minipill in a double-blind, randomized study conducted in Sweden and Finland.[23] Overall, the study results show that, with both preparations, the effect on lipids appeared to be minimal. No effect was observed on LDL cholesterol and apolipoprotein B, and there was only a small decrease in total cholesterol, triglycerides, HDL cholesterol, and lipoprotein-a. While a decrease in HDL cholesterol may be perceived as unfavorable, the global results of this study are reassuring, since the decrease in HDL cholesterol is probably too slight to significantly influence the cardiovascular risk, while a greater impact seems to be connected with the reduction in lipoprotein-a.

In order to evaluate the effect on carbohydrate metabolism of two POPs containing either 75 μg DSG or 30 μg LNG, a double-blind, randomized, multicenter study was carried out recently in Finland.[24] Plasma glucose and insulin after an oral glucose-tolerance test and glycosylated hemoglobin were utilized as parameters of carbohydrate metabolism. Overall, the effect was minimal with both medications, with a trend for higher glucose and insulin values for the LNG group. None of the changes were thought to be of clinical importance.

Another double-blind, randomized study comparing the effects on hemostasis of DSG and LNG-only pills, indicated that the changes observed in several parameters

TABLE 5. Changes in procoagulatory and anticoagulatory factors under DSG and LNG POPs

Hemostatic parameter		Treatment period 3	Treatment period 7	Posttreatment
Procoagulatory factors				
Factor VII activity	DSG	−4.8	−8.1[a]	−8.7
	LNG	−7.6	−6.8[b]	+2.2
Prothrombin fragment 1 + 2	DSG	−7.8	−14.0[a]	−7.1
	LNG	+0.6	−6.7	−10.1[a]
Anticoagulatory factors				
Protein S	DSG	+9.1	+10.0[c,d]	+7.7[b,d]
	LNG	−2.3	−1.8	−1.8

SOURCE: Winkler *et al*.[25]
[a] $P < .05$.
[b] $P < .01$.
[c] $P < .001$ vs. baseline value.
[d] $P < .005$ vs. LNG.

TABLE 6. Changes in profibrinolytic factors under DSG and LNG POPs

Hemostatic parameter		Treatment period 3	Treatment period 7	Posttreatment
Profibrinolytic factors				
Plasminogen activity	DSG	−2.0	−7.7	−7.8[a]
	LNG	−4.0	−8.1[b]	−6.6[c]
Tissue plasminogen activator	DSG	+21.1	+12.5	+10.5
	LNG	−3.5	+23.9	+28.0[c]
Plasmin–antiplasmin complex	DSG	+4.5	+4.3[d]	−6.0[d]
	LNG	−0.4	−17.4	−12.9

SOURCE: Winkler et al.[25]
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$ vs. baseline value.
[d]$P < .005$ vs. LNG.

of the coagulation and fibrinolytic system, including newer assays considered to be more predictive of a prothrombotic state, were small and in the direction of reduced activity of procoagulation,[25] as shown in TABLES 5 and 6.

EFFECTS ON LACTATION

Estrogens are generally believed to reduce the quantity of milk produced by lactating women and adversely affect milk composition.[26] In women taking Cerazette, etonogestrel is secreted into breast milk by passive diffusion, giving milk drug levels of 98–144 pg/mL;[27] the quality and the main nutrient content of breast milk are not affected to any significant degree, with no impact on the growth and development of infants followed up to the age of 2.5 years. Since breast-feeding alone is an effective form of contraception, provided that it is exclusive, or even partial, but with a sufficient number of breast-feedings per day and with suckling episodes of long duration,[28] a DSG-only pill, consistently inhibiting ovulation at a dose of 75 μg daily, offers an effective hormonal alternative to women wishing to continue partial breast-feeding for many months without running the risk of an unwanted pregnancy.

CONCLUSIONS

Progestin-only pills have been in clinical use for many years, yet they have a limited acceptability among both women and doctors, and a very low percentage of use. Although different progestins, such as NET or LNG, have been used, the mechanism of action, with an extremely low dosage utilized, seems to be strictly related to individual susceptibility: some women under POPs do not ovulate, while other subjects maintain a normal ovarian function, with the contraceptive effectiveness determined, in the latter group, by peripheral mechanisms, such as mucus hostility or endometrial changes. This explains why the use-effectiveness of the method is significantly lower than that of COCs, and why timing of tablet ingestion and woman compliance are crucial in this respect.

Women who cannot tolerate the combined pill or who exhibit important, even if transient, contraindications to the use of estrogens, could only rely upon long-acting, progestin-only methods, such as injectable, implantable, and, in recent years, intrauterine systems, for an effective hormonal contraception.

For this reason, there is a need for an oral progestin-only preparation that combines high effectiveness with a low incidence of side effects. The development of a minipill based on the use of the higly potent and selective synthetic progestogen, desogestrel, at a daily dose of 75 μg, seems to meet these criteria.

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