

## The endometrium and hormonal contraceptives

**Giuseppe Benagiano<sup>1</sup>, Alessandra Pera and Francesco M.Primiero**

Istituto Superiore di Sanità and Ist Institute of Obstetrics & Gynaecology,  
University 'la Sapienza', Rome, Italy

<sup>1</sup>To whom correspondence should be addressed

**Contraceptive progestogens have a series of effects on the endometrium that depend on the existence of oestrogen priming and therefore on the time of administration, the route through which the hormone is released to the body (systemic or locally *in utero*) and the available daily dose.** The effects of a contraceptive progestogen can be divided into two main categories: changes in the endometrial structure and vascularization and alterations of the menstrual bleeding pattern. Whereas orally administered progestogens usually cause endometrial decidualization and an important stromal reaction, the i.m., or local, intrauterine delivery is more apt to cause atrophy. Finally, all progestogens, when given alone at contraceptive doses (and irrespective of their mechanism of action), cause some disruption of menstrual bleeding patterns. This is maximal with injectable, long-acting progestogens, such as depot-medroxyprogesterone acetate and norethisterone enantate.

**Key words:** bleeding irregularities/contraceptive progestogens/endometrium/hormonal contraception

### Introduction

It is well known that the endometrium is one of the most sensitive target organs for sex steroids, with oestrogens being potent stimulators of the proliferative activity and progesterone limiting this activity and transforming the oestrogen-primed cells into a structure functionally prepared for nidation.

Due to the interactions between oestrogens and progestogens, the topic 'endometrium and hormonal contraceptives' is at the same time fascinating and multifaceted. Therefore, by necessity the discussion needs to be restricted to the effect of contraceptive progestogens when given alone. Within this context two subjects seem to have special relevance: on the one hand, the effects induced on the endometrium by either the systemic administration, or the local delivery, of contraceptive progestogens and on the other hand, the consequences that progestogens, when given alone, have in determining menstrual bleeding patterns.

It is fair to state that, ever since Pincus and his group (Rock *et al.*, 1956) started their clinical testing of orally administered progesterone as a hormonal contraceptive, the issue of the effect of contraceptive steroids on menstrual bleeding patterns took the front stage. Indeed, it was the impossibility of using progesterone without disrupting menstrual cyclicity that prompted the utilization of the newly synthesized, orally active progestogens for contraceptive purposes (Pincus, 1965). And it was fate that created the oestrogen–progestogen combination when Pincus tested norethynodrel as a hormonal contraceptive, because that steroid, due to the synthetic pathway utilized at the time, was contaminated with the oestrogen mestranol (in a 95:5 ratio) and the clinical use of this oestrogen-contaminated progestogen resulted in very acceptable bleeding patterns. Thus, the concept of an oestrogen–progestogen contraceptive combination was accidentally born (Goldzieher and Rudel, 1974).

Progestogens, however, are excellent contraceptives even when administered alone, if the woman is willing to pay the price of a certain degree of disruption of menstrual cyclicity (Benagiano, 1972; Goldzieher and Benagiano, 1982; Graham and Fraser, 1982).

Four different administration routes are utilized for contraceptive progestogens: the oral, the i.m. injection, the continuous release from polymeric rods implanted s.c. and the local delivery directly *in utero*. These modalities cause different changes to the endometrium and, therefore, produce different effects on menstrual bleeding patterns.

### **The effect of contraceptive progestogens on the endometrium**

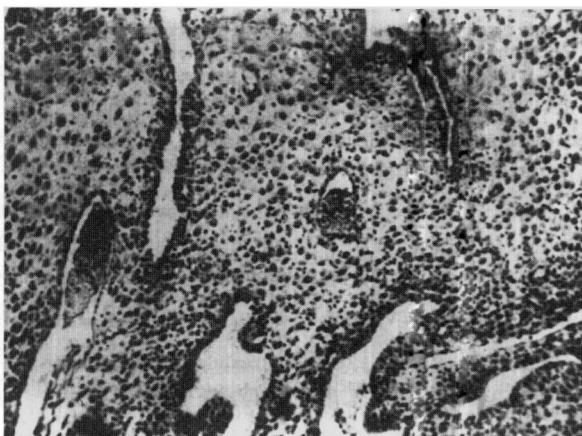
A proper evaluation of the effects that synthetic progestogens, administered alone, have on the endometrium must take into account several factors: first and foremost, the route of administration, and specifically whether the steroid is delivered locally, or systemically; second, the duration and timing of treatment; third, the presence or absence of an endogenous oestrogen priming; and fourth, the peculiar biochemical characteristics of each of the different molecules utilized clinically.

A good example of the importance of timing has been provided recently by Xing *et al.* (1983) who showed that progesterone, administered by vaginal delivery at a rate of 1.4 mg/24 h, from cycle day 2 to day 6, does not influence endometrial appearance on day 6, whereas, if it is delivered from day 7 to day 11, the endometrial appearance on day 11 is significantly altered.

It seems therefore that the endometrium can only respond to progesterone when a sufficient number of specific receptors have been induced by the oestrogen priming (Baulieu *et al.*, 1980).

### ***The effect of systemic administration***

One of the best studied synthetic progestogens is medroxyprogesterone acetate (MPA), which can be given orally or in a depot i.m. form. The oral administration



**Figure 1.** Histological appearance of the endometrium of a pre-menopausal woman treated with daily doses of 200 mg of medroxyprogesterone acetate orally for 30 days. The epithelium is atrophic, without mitoses or atypias, lying over a thick, diffuse decidualized stroma, with eosinophytic cytoplasm and vescicolous, hyperchromatic nuclei. (Previously published in Primiero *et al.*, 1987) reproduced by kind permission of CIC Edizioni Internazionali, Roma, Italy, who own the copyright.

of MPA produces effects that are dose dependent. Studying the consequences of the daily intake of 2.5, 5 and 10 mg, from day 7 to day 10, Zalányi *et al.* (1986) discovered that, on day 10, only the 10 mg dosage produced a significant decrease in stromal mitoses and a complete disruption of the pseudostratification of the glandular epithelium. The 2.5 mg dosage produced only an increase in the basal vacuolization of the glandular cells.

Some time ago our group treated a number of pre-menopausal women harbouring uterine fibroids with large oral daily doses (200 mg) of MPA for periods of up to 45 days (Benagiano *et al.* 1987). In the majority of these patients we observed, echographically, an intense endometrial growth of up to a maximum of 19 mm, and, in two cases, hysterectomy became necessary, after ~1 month of treatment, because of profuse bleeding; in three additional cases an endometrial curettage was performed.

Histologically, in all cases, an atrophic epithelium was observed, without mitoses or atypias, lying over a thick, diffuse decidual stromal reaction, with eosinophytic cytoplasm and vescicolous, hyperchromatic nuclei (Primiero *et al.*, 1987), as shown in Figure 1.

Occasionally, there was the formation of polyps covered by a thin, atrophic epithelium. Only in one case were small areas of glandular atypia observed, with the characteristics of an Arias-Stella reaction (hypersecretory glands, a pale epithelium with protrusions in the lumina, implants and proliferations) (Primiero *et al.*, 1987).

When administered as a long-acting, depot formulation (DMPA), medroxyprogesterone acetate is known to suppress ovulation for at least 3 months, after a single injection of 150 mg (Fotherby *et al.*, 1980). Contrary to what is observed after oral administration, in women given DMPA, suppression of ovarian function is paralleled by that of the endometrium, which shows either suppression or

frank atrophy, for as long as 16 weeks after the last injection. In some cases irregular endometrial growth patterns may be present up to 33 weeks after injection (Lan *et al.*, 1984).

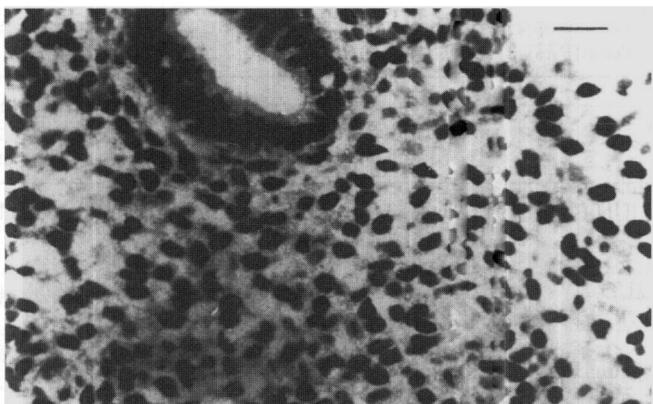
The 19-nortestosterone derivative norethisterone (NET) is one of the first progesterone analogues ever synthesized (Djerassi, 1992); when administered at the daily dose of 300 µg it can determine four different types of pharmacodynamic effects, ranging from complete suppression of both follicular and luteal activity, to normal luteal function, as determined by oestradiol and progesterone plasma concentrations. Under the influence of low doses of NET, there are significant alterations in the endometrium: the number and diameter of glands is reduced and there is a decrease in the synthesis of DNA in the cells (Landgren and Diczfalusy, 1980).

An interesting model for the study of the effect of progestogens on the endometrium is the post-menopausal woman and several investigations have now compared, in this model, the activity of a number of synthetic progestogens at different doses, following oestrogen priming (Whitehead *et al.*, 1982a,b). In general, DNA synthesis, oestradiol dehydrogenase activity and epithelial labelling index show different changes, depending on the type of molecule utilized.

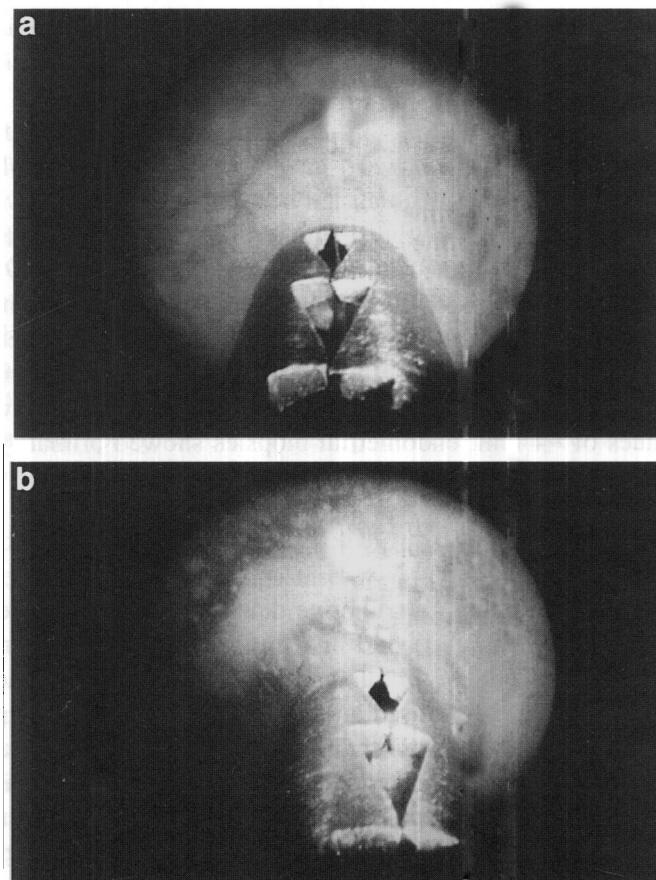
An important route of administration for contraceptive progestogens is provided by the s.c. insertion of polydimethyl siloxane (silastic) rods. This modality, developed for the continuous release of levonorgestrel (LNG), is known as Norplant and has been promoted by the Population Council (Diaz *et al.*, 1984). In spite of a great controversy created in the US by an aggressive public campaign that led to class action suits, the Norplant system remains a very useful and valid contraceptive modality. The original system utilizes five s.c. norgestrel-releasing rods, whereas the Norplant II system utilizes only two implants (Olsson *et al.*, 1988).

The effects of Norplant on the endometrium have been recently studied by Mascarenhas *et al.* (1998), who reported that, after 12 and 24 months of use endometrium was thin (<4 mm with transvaginal ultrasound), histologically inactive or weakly proliferative; in addition, Critchley *et al.* (1993) found changes in the endometrial expression of progesterone receptors. In general, despite constantly elevated peripheral LNG concentrations, the immunoreactive progesterone receptor concentration remains high, as indicated in Figure 2, but this is associated with a reduction in progesterone receptor mRNA concentrations compared with controls.

Fraser and his group have studied the endometrial vascular appearance in Norplant users, by means of hysteroscopy (Hickey *et al.* 1996). As it appears from Figure 3a, 4 months after insertion, neovascular patterns with a single vessel stem and fine branches, as well as mosaic or reticular patterns were commonly observed, whereas, with more prolonged use (Figure 3b), these patterns give rise to ecchymoses. The same group, using again hysteroscopy, compared Norplant users with women suffering from menorrhagia and was able to confirm a larger proportion of superficial dilated vessels in treated women,



**Figure 2.** Immunohistochemical staining of progesterone receptors in the endometrium of a woman bearing the Norplant contraceptive system. Notice that, despite constantly elevated peripheral levonorgestrel circulating concentrations, receptor concentration remains high. Scale bar = 50 µm. (Previously published in Critchley *et al.*, 1993, reproduced by kind permission of Oxford University Press).



**Figure 3.** Hysteroscopic appearance of the endometrial vasculature in Norplant users. (a) At 4 months post-insertion, neovascularization is evident. (b) At 6 months post-insertion, ecchymoses become manifest. The forceps shown for comparison have a 2 mm diameter. (Previously published in Hickey *et al.*, 1996, reproduced by kind permission of Oxford University Press).

**Table I.** Frequency of ectopic pregnancy in users of different types of intrauterine devices (IUD) (taken from Snowden, 1977)

Type of IUD	Effectiveness, based on conception rate (Tietze rate)	Per 100 women (Pearl index)	Ectopic pregnancies as a proportion of pregnancies occurring
All Lippes Loop IUD (4 sizes) (n = 6872)	Expected 34–51 Observed 3 Reduction of 91–94%	0.06	4.2% (1:24)
Copper-carrying IUD (Cu-7 and Cu-T) (n = 9596)	Expected 45–68 Observed 2 Reduction of 96–97%	0.05	1.7% (1:57)
Progesterone-releasing IUD (Progestasert) (n = 6813)	Expected 39–58 Observed 17 Reduction of 56–71%	0.37	21% (1:5)

compared with controls (mean diameter  $120 \pm 11.6$  versus  $74 \pm 7.2 \mu\text{m}$ ) (Hickey *et al.*, 1998).

Two other s.c. contraceptive implants have been developed. The first, Uniplant (Theramex, Monaco), is a single silastic implant containing 55 mg nomegestrol acetate with a duration of action of 1 year (Coutinho, 1993). In a series of 12 Uniplant users, endometrial changes, such as glands with inactive epithelium, absence of mitoses, irregularly formed glands in close proximity to large venous vessels, poor development of arterioles and oedema of the stroma, were common features, although in women with persisting ovulation (25% of observed cycles) a quite normal secretory endometrium was found (Devoto *et al.*, 1997).

The other implant recently developed, Implanon (Organon, Oss, the Netherlands), consists of a single rod containing 68 mg etonogestrel, and is designed to provide contraceptive efficacy for a maximum of 3 years (Olsson *et al.*, 1990). Endometrial thickness, when measured by ultrasound, was reduced, with mean values of ~4 mm; endometrial biopsies showed primarily inactive or weak proliferative endometrium (Croxatto and Mäkäräinen, 1998).

### *The effect of local delivery*

The first hormonally medicated intrauterine device (IUD), the Progestasert, was developed by Alejandro Zaffaroni and his Company, ALZA Corporation (Place and Pharris, 1974). Unfortunately, a long controversy, based on the accusation that, in the event of failure, it caused an ‘epidemic’ of extrauterine pregnancies, stopped (for all practical purposes) the clinical use of the Progestasert device, although today we can probably contend that the device was not given ‘a fair trial’.

The original observation that pointed to a disproportionate occurrence — in the event of failure — of ectopic pregnancies in users of the Progestasert was made by Snowden (1977) and is summarized in Table I. Snowden calculated that 21% of all unintended pregnancies occurring in women bearing a Progestasert were ectopic. This compared to 1.7% in the case of copper-releasing IUD. Obviously, such an effect would imply a change in the rate of passage of the

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**Table II.** Enzyme activities and protein concentration in endometrial biopsy specimens from users of a progesterone-releasing and an inert intrauterine device (taken from Hagenfeldt *et al.*, 1977)

Biochemical analysis	Control post-ovulation	IUD <i>in situ</i>			
		6-month post-ovulation		12-month post-ovulation	
		Placebo	Progestasert	Placebo	Progestasert
Alkaline phosphatase (mIU/mg DNA)	215 143–322	132 42–415	98 <sup>b</sup> 56–168	138 46–413	76 <sup>a</sup> 46–124
Acid phosphatase (mIU/mg DNA)	168 121–233	168 115–243	277 <sup>c</sup> 190–278	183 144–231	200 112–354
β-Glucuronidase (μIU/mg DNA)	2863 2351–3487	1689 976–2923	1509 <sup>b</sup> 952–2392	4003 <sup>c</sup> 2090–7664	1354 <sup>a</sup> 672–2724
Total lactic dehydrogenase (IU/mg DNA)	28.5 15.2–53.6	32.2 18.7–55.5	31.8 22.3–45.3	47.8 27.7–82.1	19.3 11.9–31.3
Total protein (mg/mg DNA)	7.3 5.2–10.1	12.0 3.4–28.2	14.8 <sup>b</sup> 10.5–20.9	11.9 6.0–16.6	7.7 4.9–12.3

Significantly different from control value: <sup>a</sup> $P < 0.001$ ; <sup>b</sup> $P < 0.01$ ; <sup>c</sup> $P < 0.05$ .

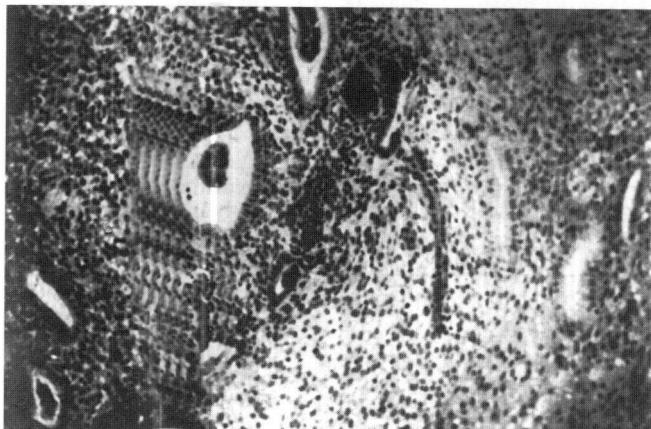
fertilized ovum in the tubes and not implicate the endometrium. This phenomenon, however, was not specifically studied at the time and researchers concentrated their efforts in the study of the mechanism of action at the endometrial level.

Two groups in particular pioneered this field, that of Hagenfeldt in Stockholm and that of Shaw in Los Angeles. Hagenfeldt *et al.* (1977; Table II) studied a number of enzymic activities in the normal endometrium and compared them to levels found in placebo devices and in medicated ones. The results of the assays pointed to a variation in the metabolism of the endometrium which could be related to the two different types of IUD. The endometrium obtained from women using the progesterone-releasing device displayed a low activity of alkaline phosphatase and β-glucuronidase, while the activity of acid phosphatase was slightly increased.

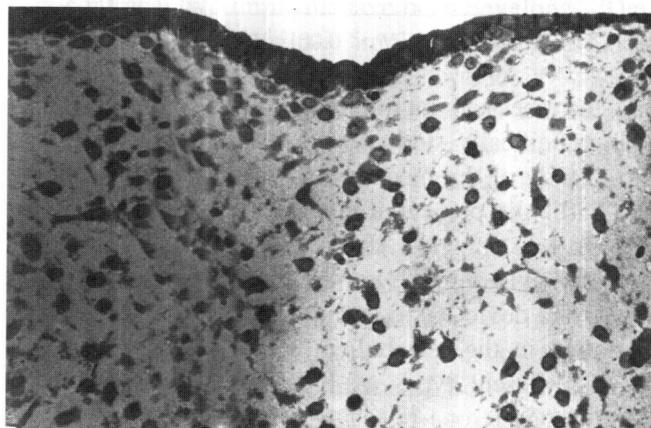
Hagenfeldt also studied endometrial histology under the influence of the progesterone released from a Progestasert device and found, as shown in Figure 4, that, with time, there was a suppression of the proliferative activity, a diffuse predecidual reaction in the stroma and changes leading to poorly developed glands, and ultimately to an atrophic endometrium (Hagenfeldt and Landgren, 1975; Hagenfeldt *et al.*, 1977).

Shaw, on the other hand, focused his attention on changes in endometrial vascularization under the influence of locally delivered progesterone (Shaw *et al.*, 1983). He found that the concentration of microscopic blood vessels was significantly lower in the endometrium exposed to progesterone released locally by an IUD, when compared to controls. Figure 5 shows a medicated endometrium: there is a clear decrease in vascularity compared to the tissue obtained from controls.

When Shaw *et al.* (1983) calculated the percentage of small vessels with



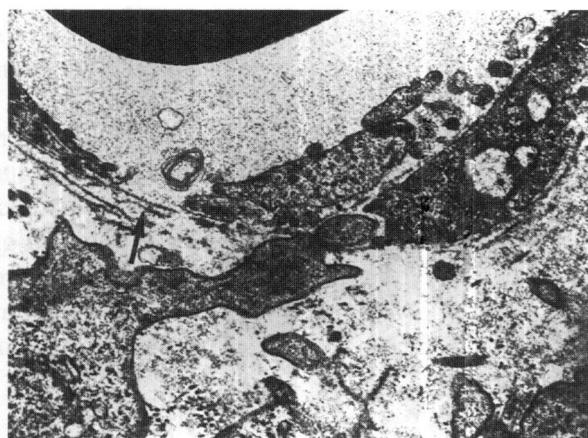
**Figure 4.** Histological appearance of the endometrium at 6 months post-insertion of a progesterone-releasing intrauterine device. Note the predecidual reaction, the upper functional and lower non-functional layers. (Previously published in Hagenfeldt *et al.*, 1977) reproduced by kind permission of the Editor, Butterworth, USA.



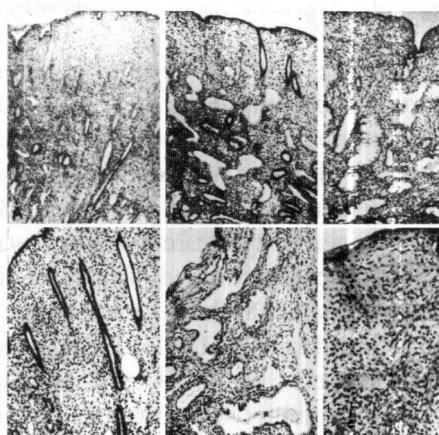
**Figure 5.** Microscopic vascular changes observed following the intrauterine insertion of a progesterone-releasing device. Note the decrease in vascularity. Original magnification  $\times 240$ . (Previously published by Shaw *et al.*, 1983) reproduced by kind permission of Mosby Inc., Orlando, Florida, USA.

defects, he found a significantly higher proportion (35%) in samples obtained from IUD bearers than in control samples (13.4%). Endothelial degeneration or necrosis were not common in the control cases, whereas they represented the majority of defects in the Progestasert users; in addition, there was no significant difference in haemostatic response to vessel injury between the IUD and control samples, although endothelial cells exhibited signs of degeneration. Figure 6 shows an electron micrograph demonstrating the endothelial damage: the arrow points to a defect between two endothelial cells.

Finally, our own group studied more than 10 years ago, the fate, within the endometrium, of the progesterone released by the device (Ermini *et al.*, 1989). Using devices releasing  $^{14}\text{C}$ -labelled progesterone, we carefully dissected the endometrium following hysterectomy, 3 months after the insertion, and analysed



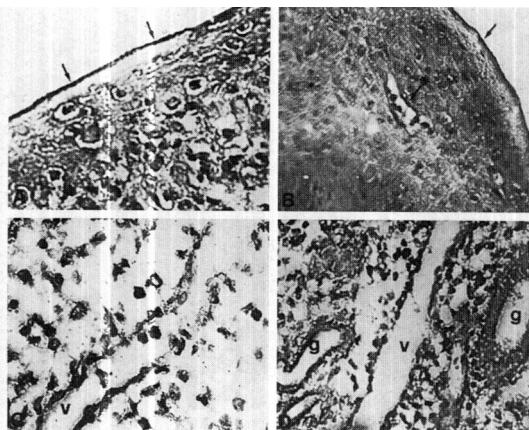
**Figure 6.** Electron microphotograph of the endometrium under the influence of progesterone released from an intrauterine device. The arrow points to a defect between two endothelial cells, which show signs of degeneration typically observed in defective blood vessels. (Previously published by Shaw *et al.*, 1983) reproduced by kind permission of Mosby Inc., Orlando, Florida, USA.



**Figure 7.** Morphological appearance of the endometrium under the influence of a progesterone-releasing intrauterine device. The upper three microphotographs show the situation during early proliferative phase and early and late secretory phases, in an area adjacent to the device. (Original magnification  $\times 70$ .) The lower left photographs show the endometrium at a distance from the device during proliferative and secretory phases. The right photograph demonstrates the decidualization of the stroma. (Original magnification  $\times 140$ .) Detail of upper far left section at original magnification  $\times 250$ . (From Ermini *et al.*, 1989, reproduced by kind permission of Oxford University Press).

its appearance, directly under the device and at progressive distance from it. Figure 7 shows the morphological appearance of the endometrium under the influence of a Progestasert. The number of glands is small, the size is small and the glandular epithelial height is low. Furthermore, the part of the endometrium adjacent to the device shows a predominance of decidual changes. The stroma obtained from the superficial layer, in contact with the IUD, shows vessels with a narrow lumen, which sometimes is completely absent; finally, the interstitial tissue is clearly oedematous.

The tissue distribution of [ $^{14}\text{C}$ ]progesterone and/or its metabolites released in



**Figure 8.** Tissue distribution in the early proliferative phase by autoradiography of  $^{14}\text{C}$ -labelled progesterone released *in utero* from a Progestasert device. Notice the intense positive uptake of the label (arrows) in the superficial layer (**A**) and in the endothelial cells of vessels (\*) adjacent to the intrauterine device (**B**). Original magnification  $\times 70$ . Note also very strong positive reaction in the stroma and in the endothelial cells of vessels (V) of section (**C**) and the glandular epithelium (g) of section **D**. Original magnification  $\times 140$ . (From Ermini *et al.*, 1989, reproduced by kind permission of Oxford University Press).

*utero* is documented in Figure 8: Progesterone is readily absorbed by the epithelium in the area directly adjacent to the device, as indicated by the intense positive uptake of the  $^{14}\text{C}$  isotope.

More recently a new device has been developed, which releases LNG and has been marketed under the trade name of Mirena (Schering A.G., Berlin, Germany). LNG is released into the uterine cavity at a constant rate of  $\sim 20\ \mu\text{g}/24\ \text{h}$ . Once delivered, levonorgestrel is quickly absorbed via the capillary network in the basal layer of the endometrium and can be detected in the plasma 15 min after the insertion of the device (Luukkainen, 1991). Plasma concentrations of LNG are fairly stable and range between 100 and 200 ng/l, although marked individual variations exist. These concentrations, however, are lower than those measured after orally administered minipills or the insertion of Norplant devices and, in general, do not cause ovarian suppression (Barbosa *et al.*, 1990).

The intrauterine delivery of LNG strongly suppresses endometrial growth (Silverberg *et al.*, 1986; Perino *et al.*, 1987): after only a few weeks from the insertion, the glands of the endometrium show almost complete atrophy, the stroma becomes inactive, cylindro-cubic, monostratified and without mitoses; there is a decrease in the number of glands and glandular cells, cubical or flat epithelia, decidualized stroma and an infiltration with inflammatory cells. Capillaries are dilated, with an occasional thrombosis.

Vascular changes include a thickening of arterial walls, suppression of the spiral arterioles and capillary thrombosis. An inflammatory reaction characterized by an increase in neutrophils, lymphocytes, plasma cells and macrophages has been also described (Zhu *et al.*, 1989).

Endometrial changes are uniform within three cycles after the insertion of the system and no further histological modification takes place over the long term (Silverberg *et al.*, 1986). Luukkainen *et al.* (1986) believe that the potent mucosal

suppression caused by Mirena may be explained by the regulatory action of LNG on endometrial oestrogen receptors. After removal of the system, morphological changes in the endometrium revert to normal within the first month (Nilsson and Lähteenmäki, 1977).

An important feature of a hormonal contraceptive method that acts only locally is the avoidance of oestrogen deficiency, which, in turn, prevents osteoporosis even over long-term use. In this respect, Luukkainen and Toivonen (1995) showed that circulating concentrations of oestradiol in individual women with a levonorgestrel-releasing IUD are in the range of normal menstrual cycles, even in subjects who become amenorrhoeic.

### **The effect of contraceptive progestogens on menstrual cyclicity**

Because the route of administration directly influences the action of a progestogen on the endometrium it should not be surprising that it also causes different effects on menstrual bleeding patterns.

#### *Effect of systemic administration*

Starting with the oral route, the major studies reporting data on the results of clinical trials utilizing progestogen-only minipills, are summarized in Table III, modified from Kovacs (1996).

Menstrual disturbances in users of minipills, on the average, account for some 25% of all discontinuations; the most common irregularities consist in an increased frequency of bleeding, lengthened cycles, spotting and breakthrough bleeding (Hatcher *et al.*, 1988; Speroff and Darney, 1992). Of particular concern for individual women is the unpredictability of the menstrual cycle length.

There are three randomized studies in which both progestogen-only minipills and combined oral contraceptives have been compared (Vessey *et al.*, 1972; Paulsen *et al.*, 1974; WHO, 1982). In all three, disruption of menstrual cyclicity was greater in minipill users.

As summarized in Table IV, also taken from Kovacs (1996), more acceptable patterns have usually been observed in lactating women using progestogen-only minipills, an important observation because these pills do not interfere with lactation (McCann *et al.*, 1989).

As indicated above, the second way of administering a contraceptive progestogen is to inject it in a long-acting form. Two preparations are available on the market: the already mentioned DMPA, commercially known as Depo Provera (150 mg given every 3 months) and Noristerat (norethisterone enantate, 200 mg given every 2 months). When these drugs are administered, there is invariably a profound disruption in the menstrual cyclicity (Goldzieher and Benagiano, 1982; Benagiano and Primiero, 1983a,b).

The WHO Task Force on Long-acting Systemic Agents for the Regulation of Fertility (1986) followed women given DMPA over time; dividing the observation

**Table III.** Studies on bleeding patterns in progestogen only-pill users (modified from Kovacs, 1996)

Reference	Country study based in	No. of women	Results
Vessey <i>et al.</i> (1972)	Yugoslavia	74/NG 76/NETA 77/CAN 80/MA	5.4 1.6 2.1 2.7
Korba and Paulson USA (1974)		2202/NGL	Discontinuation rate at 1 year because of bleeding
Hawkins and Bentser (1977)	England	200/NET 182/CMA 184/MA	13.7% discontinued because of bleeding; 70.3% had 21–45 day cycle
Lawson (1982)	UK, New Zealand, Jamaica	913/NET	Discontinuation rate at 1 year because of menstruation disorders
WHO (1982)	India Yugoslavia	130/NET 128/LNG	Breakthrough bleeding: 24% in cycle 1, 7.2% in cycle 12
Vessey <i>et al.</i> (1985)	England	1746/NET 555/NG 459/EDD 405/LNG	One-quarter in both groups discontinued after 1 year because of bleeding
Broome and Fotherby (1990)	England	189/NET 27/LNG 62/EDD	54.3% of NET discontinuations and 62.8% discontinuations of other progestins
Ball <i>et al.</i> (1991)	England	23/NET 23/LNG	47.5 overall discontinuation rate because of bleeding
Bisset <i>et al.</i> (1992)	Scotland	1.24 1.28	No. of bleeding episodes per month
		369/NET 332/EDD 195/NG 146/LNG	15% discontinued because of bleeding. No difference between groups

NG = norgestrel; LNG = levonorgestrel; NET = norethisterone; NETA = norethisterone acetate; EDD = ethynodiol diacetate; CMA = chlormadinone acetate; MA = megestrol acetate.

**Table IV.** Bleeding patterns in breast-feeding women using progestogen-only pills (modified from Kovacs, 1996)

Reference	Country study based in	No. of women/progestin used	Results
Apeloso and Veloso (1973)	Philippines	99/LNG	3% discontinued because of bleeding
West (1983)	Scotland	84/NET	4.8% discontinued because of irregular bleeding
McCann <i>et al.</i> (1989)	Argentina	250/LNG	1.6% discontinued because of bleeding
Moggia <i>et al.</i> (1991)	Argentina	241/NG	36% intermenstrual bleeding
Dunson <i>et al.</i> (1993)	Multicentre	4088/NG	4.9% discontinued because of bleeding

NG = norgestrel; LNG = levonorgestrel; NET = norethisterone.

**Table V.** Proportion of women experiencing different types of bleeding pattern with depot-medroxyprogesterone, alone (Depot) or in combination with oestradiol cypionate (Cyclofem) (from Newton *et al.*, 1994)

Group	Days	Amenorrhoea (%)	Irregular bleeding (%)	Prolonged bleeding (%)	'Acceptable' pattern (%)
Untreated	1-90	1.3	4.5	2.6	90.3
	271-360	1.6	8.6	4.3	85.1
Cyclofem	1-90	0.1	39.6	20.8	43.0
	271-360	2.3	13.6	10.1	70.0
Depot	1-90	10.6	46.0	43.4	9.0
	271-360	38.6	17.9	16.5	8.3

into 3-month reference periods, they found that, during the first period, only 10% of users showed regular menstrual patterns; on the other hand, in the fourth reference period, amenorrhoea was present in 40% of all women. Great inter- and intra-individual differences exist, resulting in a totally unpredictable bleeding pattern that has been labelled 'menstrual chaos'. There is no tendency to normalization with prolonged use. Most clinical trials report a frequency of amenorrhoea at 1 year of between 30 and 60%, with an increase that approaches 90% in very long-term users (Benagiano and Primiero, 1983a).

Belsey (1988), using the WHO classification of '90-day reference periods', compared patterns in users of eight different hormonal contraceptive methods with those in women utilizing a natural method of family planning. Subjects given combined oral contraceptives had the most regular bleeding patterns; progestogen-only minipill users had more frequent, longer bleeding episodes, but, contrary to widely held beliefs, produced fewer spotting days. Women injected with DMPA had the most unpredictable bleeding patterns (Newton *et al.*, 1994).

These data were further elaborated by Newton *et al.*, 1994 and are shown in Table V: it can be seen that, in controls, the proportion of regular cycles ranges between 90 and 85% of all cycles. In contrast, in users of Depo Provera this percentage decreases to less than 10%. The addition of an oestrogen to Depo Provera, as in the monthly injectable Cyclofem, also known as Cyclo Provera, significantly improves the regularity of menstrual bleeding.

More acceptable bleeding patterns seem to be associated with Noristerat, with significantly fewer women experiencing amenorrhoea (30% at 12 months and 40% at 24 months) or discontinuing for that reason (WHO, 1983). This difference may be due to the fact that inhibition of ovulation is constantly achieved with Depo Provera during the 90 day interval between injections, whereas with Noristerat some ovarian activity may become apparent during the second month after the injection.

Bleeding disturbances also occur when utilizing the continuous release from s.c. implanted silastic rods (the Norplant system) providing contraceptive protection over 5 years.

In a large clinical trial in China, Meng and Gu (1996) found a relatively low

incidence of bleeding disturbances with a very good continuation rate. In particular, bleeding irregularities occurred in 13% of all cycles. In the first year the average duration of a bleeding and spotting-free interval was around 20 days; for those women who completed the first year, the number of bleeding days showed a significant increase. However, normal patterns also increased with time, from 7.8% at 1 year, to 32.3% at 5 years.

Another long-term study confirmed that bleeding patterns in the majority of women using Norplant are characterized by frequent, irregular and/or prolonged bleeding during the first 12 months of use (Faundes *et al.*, 1978). Unlike other progestogen-only methods, bleeding patterns and most discontinuations for menstrual reasons occur during the first year (Sivin *et al.*, 1983; Olsson *et al.*, 1988). The progressive improvement in bleeding patterns is probably determined by the return of ovulatory or ovulatory-like cycles, which, in turn, reflects the decrease in LNG release rate. This has been confirmed in a study specifically designed to correlate bleeding patterns with endocrine response in 15 women who had been using Norplant II for more than 3 years. All subjects were monitored with hormonal assays and ultrasonography for the assessment of ovarian function. Among these women, six had ovulatory-like patterns, six had signs of follicular activity, and three signs of inadequate luteal activity, with regular menstrual cycles in all cases (Odlind and Fraser, 1990).

More recently, Faundes *et al.* (1998), looking at oestradiol and progesterone plasma concentrations and endometrial development (as assessed by vaginal ultrasound) among Norplant users with bleeding complaints, found that almost all women with bleeding problems had anovulatory cycles, with lower oestradiol concentrations and a thin endometrium. A good correlation existed with increasing oestradiol concentrations and longer bleeding-free intervals, but not with endometrial thickness, suggesting that oestrogens have a haemostatic effect which is not mediated or manifested by endometrial growth.

When compared with Norplant users, women implanted with Implanon had more amenorrhoea, and slightly more infrequent, frequent and prolonged bleeding; the difference, however, was only statistically significant for amenorrhoea (Affandi, 1998).

A difficult issue, peculiar to this system, is the assessment of continuation rates, especially in developing countries. Implant retrieval has come under close scrutiny, because a trained physician is required for extraction and accusations have been made that women have been forced to keep the devices even in the presence of bleeding disturbances, because physicians were unwilling to proceed with the extraction.

### *Effect of local delivery*

Prolonged spotting and other menstrual irregularities are common in the early months after Mirena insertion; however, as time proceeds, a major reduction in menstrual blood loss appears to be a constant picture, with ~20% of all users being amenorrhoeic by the end of the first year after insertion. As already pointed

out, amenorrhoea, when present, is only due to the direct suppression of the endometrium exerted by LNG, since no significant difference can be appreciated in terms of LNG plasma concentrations and ovarian activity between amenorrhoeic and regularly cycling women (Nilsson *et al.*, 1984). The overall picture emerging from the clinical use of Mirena is positive: in a long-term study, Andersson *et al.* found, at 5 years, an extremely low pregnancy rate of 0.3 per 100 woman-years, with a total expulsion rate below 5% and bleeding problems in some 11% of the women (Andersson *et al.*, 1994).

## Conclusions

In conclusion, there is no doubt that progestogens can have a profound contraceptive effect through their influence on the endometrium. Some of the most effective contraceptive methods available, such as Depo Provera, Norplant or the LNG-releasing IUD Mirena, utilize a progestogen as the active component. What is even more interesting is the fact that all these methods produce a true 'endometrial contraception'; this is proven by the very high effectiveness of Mirena, which does not substantially alter ovarian function.

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