Short-Acting Hormonal Contraception: The Pills, the Patch, and the Rings

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7.1 The Beginning

Ludwig Haberlandt (1885–1932) is known as the father of hormonal contraception. In 1921, he carried out experiments on rabbits, and he demonstrated a temporary hormonal contraception in a female by transplanting ovaries from a second, pregnant, animal [1].

Russell Earl Marker (March 12, 1902–March 23, 1995) founded a steroid industry in Mexico. In 1937, he discovered the first practical synthesis of progesterone when he successfully made synthetic progesterone from chemical constituents found in Mexican yams.

Carl Djerassi refined the method of synthetic progesterone manufacturing, and by chemically modifying the substance ethisterone he developed norethindrone which had a higher biological activity. The first progestin to be patented was a very similar substance—norethynodrel.

In 1951, Gregory Pincus (1903–1967) received a small grant from the planned parenthood federation of America to begin research into hormonal contraceptive research. His lab confirmed earlier research that progesterone and progestins induced anovulation.

Women's right activist Margaret Sanger facilitated a much larger grant in 1952 from her rich friend Katherine McCormick. In total Katherine McCormick granted two million dollars towards the development of the oral contraceptive pill—an enormous amount of money at that time.

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In 1953 and 1954 trials were performed with different progestins on infertile patients as contraception was illegal at the time. The physician in charge of the trials was John Rock, a catholic gynecologist who performed the trials at his clinic. Eventually Puerto Rico was therefore chosen for the first clinical trials into the contraceptive effects. Results were mind-blowing. The combination of a progestin and an estrogen gave close to 100% protective effect against pregnancy. Studies were expanded to Mexico and included thousands of women. One of the main effects of the pill was a reduction in menstrual flow and menstrual pain. In 1957, the pill was registered in the USA for these indications. The pill "Enovid 10 mg" manufactured by Searle contained 0.15 mg of the synthetic estrogen mestranol and 9.85 mg of a progestin very closely related to the first patented progestin developed by Carl Djerassi. The contraceptive effect was a "side effect." In less than 2 years, close to half a million women had taken the pill—presumably quite often due to the "side effect." In 1957, the pill was approved for contraception in the USA and thereby the first contraceptive pill had been approved.

7.2 Early Development of the Estrogen Component

In the 1960s, the first reports on serious adverse events in pill users were reported. They included venous thromboembolisms. It became evident in the 1970s that the estrogen was the culprit of these serious side effects. Estrogen doses were rather quickly lowered, and a pill with 30 μg of ethinyl estradiol (EE) was registered as early as in the 1970s. However, pills with 50 μg EE dominated the market until the 1980s and are still available in some countries. Attempts were made with estradiol as the estrogen component as early as the 1970s and research continued onwards with other—WHO performing such studies (1980 WHO two combined oral contraceptives containing the same progestogen, but different estrogens. World Health Organization Task Force on Oral Contraception (gestagen norethisterone acetate)). However, no such preparation reached the market—mostly due to poor bleeding control.

The ethinyl estradiol has evident advantages in oral contraception. It is easily absorbed and has a long half-life (several days compared to hours with estradiol) due to resistance to degradation by 17 β-dehydrogenase. It does not bind to SHBG and therefore circulated freely. In addition, it binds to the estrogen receptors with high affinity. This in turn leads to strong biological effect on target organs such as the uterus for a better bleeding pattern, but also on protein production in the liver. Lowering the dose of EE in pills below 30 μg has been shown to lead to less favorable bleeding patterns with more breakthrough bleeding [2].

The effect of EE on the liver can if fact lead to desired effects in treatment of hirsutism or acne but also to undesired effects such as risk of venous thromboembolism. Thus, the effect of estrogen in a combined hormonal contraceptive preparation depends on type of estrogen foremost and dose of estrogen only secondly. Understanding the difference in biological effect between ethinyl estradiol and estradiol is fundamental when choosing the right combined hormonal contraceptive for every individual woman.

7.3 Progestin Development

Although progestins are essentially artificial or synthetic progesterones, they differ in potency and receptor affinity. Progestins bind not only to the progesterone receptor but may also have an effect on the androgen receptor. The earliest preparations had high doses of progestins in effect causing very low naturally circulating levels of estrogen due to ovarian inhibition. The added estrogen was initially in part there to compensate for these low natural estrogen levels. It became evident that such high doses of progestins were not necessarily needed for anovulation and doses were subsequently lowered. Progestins were patented by the companies when producing contraceptive pills and subsequently used in the different formulations from that same company. The contraceptive effect and ovulation inhibition were the factors that interested the most and that were evaluated in the clinical trials. Side effects were recorded but very similar for all progestins [3].

Attempts at synthesizing the "perfect" progestin are still ongoing. Ideally a progestin should be potent and inhibit ovulation to have a high contraceptive efficacy. Furthermore, it should be selective and have a stabilizing effect on the endometrium to reduce side effect and breakthrough bleeding. Preferably, the progestin should also affect mood less than our naturally occurring progesterone. As combined hormonal contraceptives are taken orally every day, the half-life of progestins and the effect of the half-life on effectiveness in typical use have discerned more interest.

7.4 Combined Hormonal Contraception

7.4.1 Administration-Dependent Differences Between Pill, Patches, and Rings

Short-acting reversible contraception consists of daily pills, a weekly patch, or monthly rings. These naturally have different modes of absorption leading to differences in plasma concentration over the duration of the administration (Fig. 7.1) [4].

Comparisons of patches and rings with COCPs have been evaluated in repeated Cochrane reports. Plasma concentration of EE is higher with the patch. A higher proportion of women using the patch report estrogen-dependent side effects such as breast tenderness [5]. Patch skin reactions and detachment are rare but occur and may lead to early discontinuation [5]. For ring users an increase in vaginal discharge has been established. This may be considered as "less vaginal dryness" or "increased discharge" [5]. Ring users appear to be more satisfied than COCP users [5]. A pill needs to be taken every day. Patches and rings may have the advantage of more stable concentrations of EE and progestins. No difference in contraceptive effectiveness has been shown for the methods [5]. It has been shown that patches and rings lead to more favorable bleeding pattern than a pill containing 30 μg of EE [5]. In the case of the rings, this is established in spite of a lower plasma concentration of EE.

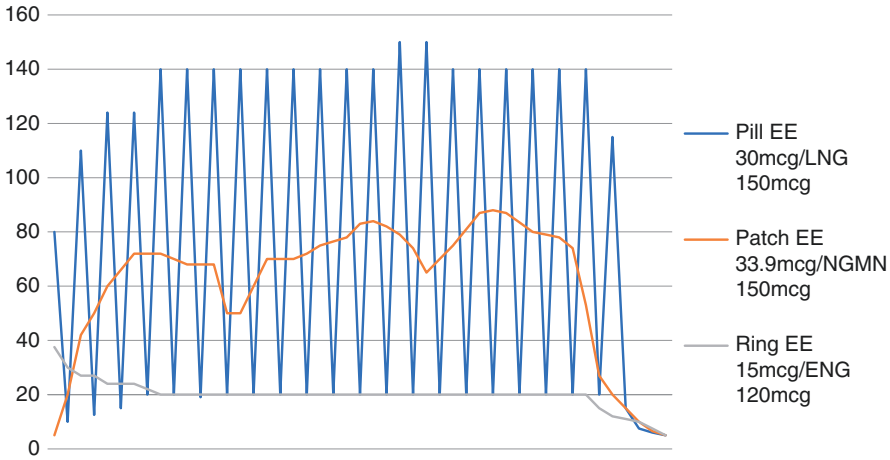

Fig. 7.1 Estrogen concentration depending on mode of administration. Concentration in picograms per milliliter over a treatment cycle of 21 active treatment days. Last measurement on day 24. Levels are rounded off and levels in figure may therefore differ from actual levels. The figure serves to give the reader an idea on differences depending on mode of administration. *EE* ethinyl estradiol, *LNG* levonorgestrel, *NGMN* norelgestromin, *ENG* etonogestrel. (Modified from [4])

7.4.2 Contraceptive Effectiveness

Recently, it has been shown that contraceptive efficacy may not only depend on the ability of the progestin to induce anovulation in a classic 21/7 regimen.

Several factors may affect effectiveness in real life. Such factors may be:

1. User dependent
2. Regimen dependent
3. Dependent on the intrinsic characteristics of the progestin

7.4.2.1 User Dependency

Several studies have shown that younger women have higher failure rates when using oral contraception. This in turn may of course depend on younger women being more fertile. However, recent studies suggest that younger women seem to forget pills more often [6, 7]. Thus, short-acting reversible contraception may not be the best contraceptive method for young women.

7.4.2.2 Different Regimens of Use

The pill was designed to produce a "natural bleeding" once a month. The original regimen entailed taking 21 days with active pills and then having a pill-free break of 7 days. As hormones are withdrawn, this induces a predictable withdrawal bleeding. Thus, the bleeding is completely artificial and is due to the rapid lowering of hormones. Some manufacturers include seven placebo pills instead of recommending a pill-free break.

During the seven pill-free (placebo) days, the follicle suppression ceases and the follicles start to mature, producing endogenous estrogen which makes the endometrium proliferate. This in turn creates a thick enough endometrium to be shed after the 21 days. If pills are forgotten after the pill-free break, the follicles mature even more. For women with a short menstrual cycle, a pill-free break of more than 7 days may be enough for ovulation to happen. An experimental study showed that ovulation occurs in approximately 10% of women if the pill-free break is extended to 10 days [8]. In opposite, with a shorter pill-free break, we ought to achieve less maturing of follicles, less growth of the endometrium, and thus less chance of ovulation and less bleeding. This has now been verified in numerous studies which show that follicles become smaller and that fewer women ovulate if the pill-free (placebo) break is shortened to 4 days [9, 10].

7.4.2.3 Importance of the Progestin Content

As short-acting reversible contraception is dependent on daily, weekly, or monthly administration, the half-life of any progestin in the contraceptive may affect how long it is possible to forget the pill, patch, or ring. It has been shown that the half-life of the progestin may affect the rate of anovulation and thereby contraceptive effectiveness in real life. A progestin with a longer half-life may be more permissive to forgetfulness.

Half-lives of different progestins vary greatly (see Table 7.1).

That regimens with a shorter pill-free break (or a placebo pill intake) and formulations with a progestin with a longer half-life improve contraceptive effectiveness in typical use has been shown in a large prospective study [11].

If shortening the pill-free break increases effectiveness, one might subsequently wonder if abstaining from a break would in fact increase effectiveness further. To this date, no study proving this has been published. Often extended regimens are divided into continuous regimens when no break is made, extended regimens with a planned break—often after 3 months or extended flexible regimens when women can choose to make a break or are told to make a break after a certain number of days with bleeding. A Cochrane review of extended and continuous regimens including 12 randomized trials concluded that there is no difference in compliance between traditional 21/7 regimens and extended or continuous regimens. The studies that reported tolerance found that there was less headache, genital irritation, tiredness, bloating, and menstrual pain in the extended or continuous groups. Although several studies find that spotting and bleeding may be more frequent initially in the extended and continuous regimens, these symptoms often disappear or

Table 7.1 Progestin half-lives in hours in selected commonly available progestins

Dienogest	9.1
Desogestrel	11.2
Levonorgestrel	14.8
Drospirenone	31
Nomegestrol acetate	48

subside with time and that women resulting in a more acceptable bleeding pattern than the 21/7 regimens [12].

7.4.3 Progestin-Only Pills

Progestin-only pills are traditionally taken without a pill-free (placebo) break. The mechanism of action depends on the dose of the progestin.

7.4.4 Low-Dosed Progestin Pills

Classic progestin-only pills are low dosed. The suppression of ovarian function is individual depending on type and dose of the androgen in addition to individual effects. Ovulation has been shown to be inhibited in 40–67% of women [13]. If ovulation is not inhibited, the low-dosed progestin-only pills still affect cervical mucus and thus prevent sperm entry into the uterus. In addition, the tubal transport of the egg is affected and the endometrial lining becomes thin and inhospitable for the fertilized egg [14].

The effect on cervical mucus is short acting. Thus, the pills need to be taken more or less the exact time every day within a margin of 3 h. If this timing is missed, back-up protection is needed. Naturally, the lack of ovulation inhibition and the low tolerance for forgetfulness lower the effectiveness of the low-dosed progestin pills.

Low-dosed progestin pills affect tubal transport—often without affecting ovulation. In addition, implantation in the thin endometrium is affected. This leads to a slightly higher risk of ectopic pregnancy in women taking these pills [15]. In most countries, today medium-dosed progestin-only pills are available, and therefore the market share of the classic low-dose pills has dwindles. However, in the USA no medium-dosed pill has been registered until very recently.

7.4.5 Medium-Dosed Progestin Pills

Medium-dosed progestin-only pills induce ovarian inhibition and thereby follicles do not mature [16, 17]. Recently, a new medium-dosed pill with 4000 mg non-micronized drospirenone has entered the market. Comparative studies have been performed showing comparable ovarian inhibition [18]. Studies show that medium-dosed progestin-only pills maintain ovarian activity with estradiol levels corresponding to early follicular phase [17].

The medium-dosed desogestrel pill is currently registered in a continuous regimen, whereas the drospirenone pill is registered in a 24/4 regimen. A comparative study shows that the number of bleeding days is reduced with the 24/4 regimen during the first 3 months. Thereafter, the total number of bleeding days is similar

(Exeltis, data on file). However, the drospirenone pill in the 24/4 regimen induces a planned bleeding, whereas all bleeding in a continuous regimen may be considered as unplanned.

7.5 Androgenicity and Anti-androgenicity

Androgenicity may affect the added health benefits and the side effect profile of combined hormonal contraception. Whereas the androgenicity and anti-androgenicity of a progestin-only product depends on the dose and the properties of the progestin itself—the androgenicity or anti-androgenicity of a combined hormonal contraceptive product depends on two mechanisms of action.

1. The type of estrogen
2. The dose of this estrogen
3. The androgen receptor action of the progestin

EE has a long half-life and as strong estrogen receptor affinity. EE is resistant to metabolism by 17β-hydroxysteroid dehydrogenase—the enzyme mainly responsible for metabolism of naturally occurring estrogens. Thus, EE circulates many times through the body before it is excreted in feces and through the gall and the urine. In the bloodstream, it is mainly bound to albumin and has very low binding affinity for SHBG. As it circulates through the liver, it affects the production of numerous proteins. EE induces production of among other proteins—the sex hormone binding globulin (SHBG). SHBG acts as a transport protein in human blood for our sex hormones. As the production of SHBG is increased, the amount of free androgens in bloodstream is decreased. Thus, an anti-androgenic effect is created. The higher the dose of EE, the more SHBG is produced and the higher the anti-androgenic effect. On the other hand, estradiol does not affect levels of SHBG as EE. Thus, the anti-androgenic effect of estradiol-based combined hormonal contraception is less.

Progestins may have an effect on the androgen receptor. They may either serve as agonists, be largely neutral, or have anti-androgenic effect by blocking the androgen receptor. Classifying a progestin androgen receptor activity may be done by different methods whereof one is studying the effect on rat prostate. If the androgen shrinks the rat prostate, it is considered anti-androgenic. The androgenicity and anti-androgenicity of common progestins are shown in Fig. 7.2.

When an anti-androgenic progestin is combined with EE, a powerful anti-androgenic effect is created. All currently available combined hormonal contraceptives containing EE are anti-androgenic. This can be shown by analyzing the effect on acne. A Cochrane review shows that although one of the least anti-androgenic EE-containing combined hormonal contraceptive pills (20 μg EE and 100 μg LNG) treats acne more effectively than placebo, the most anti-androgenic pill (35 μg EE and 2000 μg CPA) treats if far more effectively [21].

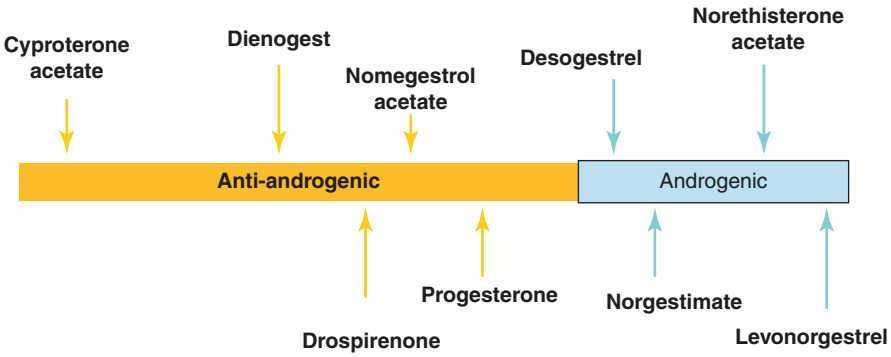

Fig. 7.2 Anti-androgenic and androgenic potency of various progestins. (Modified from [19, 20])

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