New progestagens for contraceptive use

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The progestins have different pharmacologic properties depending upon the parent molecule, usually testosterone or progesterone (P), from which they are derived. Very small structural changes in the parent molecule may induce considerable differences in the activity of the derivative. In hormonal contraceptives, progestins represent the major agent designed for suppressing ovulation and are used in combination with estrogen (E) usually ethinyl-estradiol (EE). The development of new generations of progestins with improved selectivity profiles has been a great challenge. Steroidal and nonsteroidal progesterone receptor (PR) agonists have been synthesized as well, although the latter are still in a very early stage of development. Several new progestins, have been synthesized in the last two decades. These include dienogest (DNG), drospirenone (DRSP), Nestorone (NES), nomegestrol acetate (NOMAc) and trimegestone (TMG). These new progestins have been designed to have no androgenic or estrogenic actions and to be closer in activity to the physiological hormone P. DRSP differs from the classic progestins as it is derived from spiroloactone. It is essentially an antimineralocorticoid steroid with no androgenic effect but a partial antiandrogenic effect. The antiovulatory potency of the different progestins varies. TMG and NES are the most potent progestins synthesized to date, followed by two of the older progestins, keto-desogestrel (keto-DSG) and levonorgestrel (LNG). The new molecules TMG, DRSP and DNG also have antiandrogenic activity. Striking differences exist regarding the side effects among the progestins and the combination with EE leads to other reactions related to the E itself and whether the associated progestin counterbalances, more or less, the estrogenic action. The 19-norprogesterone molecules and the new molecules DRSP and DNG are not androgenic and, therefore, have no negative effect on the lipid profile. Given their pharmacological properties, it is likely that the new progestins may have neutral effects on metabolic or vascular risks. However, this hypothesis must be confirmed in large clinical trials.

Key words: contraception/dienogest/drospirenone/Nestorone/nomegestrol acetate/trimegestone

Introduction

The progestagens or progestogens include both progesterone (P), the hormone secreted by ovary and placenta and the synthetic steroids or progestins that mimic the actions of endogenous P. The new progestagens are, by definition, progestins, and this term will be used throughout the review. Several new progestins have been synthesized in the last decade for use in both contraceptives and hormone replacement therapies (HRTs) (Stanczyk, 2002; Sitruk-Ware, 2004).

One of the main actions of P or a progestin is the secretory transformation of an estrogen-primed (E-primed) endometrium. P or a progestin prevents the over-proliferation of the endometrial tissue, but the degree to which this effect is achieved depends upon the antiestrogenic properties of the progestin and the dose and duration of treatment. As contraceptive agents, progestins with high anti-gonadotropic potency ensure suppression of ovulation and are combined with E in most hormonal contraceptives, combined oral contraceptives (OCs) or non-oral delivery systems such as vaginal rings, transdermal patches or gels. They are also used without E as progestin-only contraceptive agents also named progestin-only pills (POP).

The effects of progestins are related to interactions not only with the progesterone receptor (PR) but also with other steroid hormone receptors. Some progestins interact with the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR) or the mineralocorticoid receptor (MR). These interactions may either induce transactivation of a steroid receptor or prevent activation. In the target organ, the balance between the receptor coactivators and corepressors recruited by a progestin determines whether the overall effect of the molecule will be agonistic or antagonistic (Liu et al., 2002). All progestins bind to the PR and have the expected effect on the uterine endometrium, but each progestin has a distinctive profile of activity in other target tissues, a profile not necessarily shared by other members of the same class.

Secreted by the corpus luteum after ovulation, P has several biological actions. It maintains pregnancy through its antiestrogenic
action, preventing contractions of the uterus; it transforms the endometrium into a secretory tissue to permit implantation of a fertilized ovum; and it prevents further ovulation through its antigonadotropic action. In addition, P has an antiandrogenic effect. P competitively inhibits the action of androgen, as it is a preferred substrate to the enzyme 5α-reductase, hence preventing the conversion of testosterone into its active metabolite dihydrotestosterone (Wright et al., 1983). P also interacts with the MR; competitive binding to this receptor by P prevents its transactivation and inhibits the mineralocorticoid effect. This antagonistic effect prevents sodium retention and instead induces the excretion of sodium and water (Corvol et al., 1983).

The older progestins, synthesized in the 1960s and 1970s, were designed for use in contraceptives. For this reason, a major design target was the antigonadotropic action (Henzl and Edwards, 2000). The new progestins synthesized in the last two decades were designed with the objective of creating the ‘ideal’ progestin. It was hypothesized that a progestin with potent progestational and antiestrogenic actions on the endometrium coupled with a strong antigonadotropic effect and without any androgenic or glucocorticoid effects would produce the benefits of P without undesirable effects, such as acne, a decrease in high-density lipoprotein cholesterol (HDL-C) or bloating and water retention. In addition, other beneficial actions of P, such as its antiandrogenic and antimineralcorticoid effects, were incorporated into the design of some new progestins (Oettel and Holz, 2000; Elger et al., 2003). Antiandrogenic progestins may have several potentially beneficial effects, such as reducing endogenous androgen action and decreasing the incidence of acne or hirsutism.

In addition, when given in the presence of naturally secreted estradiol (E2) or together with a synthetic E, the final effect of a progestin on the target organs depends upon the potency of the E. The potency differences among the Es and their varying effects on the liver, which are determined by their molecular structure as well as by the mode of delivery, may change the way a specific progestin, given at a certain dose, affects not only the endometrium but also the lipid profile, the blood vessels, and, possibly, breast tissue.

**Classification: new versus older progestins**

By convention, the older progestins are divided into three generations. These molecules can be classified according to the steroid from which they derive, P, 17-hydroxyprogesterone or testosterone, which will then determine the molecular structure. (i) The first generation included norethynodrel and the nortestosterone derivatives that become active after conversion to norethisterone (NET) (Estranes). It also includes the 17-hydroxyprogesterone derivatives (Pregnanes). The second generation included norgestrel and levonorgestrel (LNG) (Gonanes), and the third generation included the LNG derivatives such as desogestrel (DSG), its active derivative etonogestrel (contained in Implanon® and Nuvaring®, gestodene (GES) and norgestimate and its active derivative, norelgestromine (contained in the new transdermal contraceptive Evra®). Most of the progestins in the first three generations were derived from testosterone. Their structures were modified to reduce the incidence of undesirable androgenic side effects but these progestins still bind to the AR, thus making it difficult to eliminate completely some unwanted androgenic side effects. (ii) Drospirenone (DRSP), dienogest (DNG), trimegestone (TMG), Nestorone® (NES) and nomegestrol acetate (NOMAc) are considered to be ‘new’ progestins, as some have only recently reached the market and others are still under development (Table I).

The new progestins have been designed to bind very specifically to the PR and not to other steroid receptors to avoid androgenic, estrogenic or glucocorticoid side effects (Kuhl, 1996a; Stanczyk, 2002; Schindler et al., 2003).

**Pharmacology of the progestins; methods of evaluation**

**Mode of action of the progestins and transactivation of the receptors**

The binding affinity of a progestin to the PR does not provide a complete portrait of steroid hormone activity at the receptor. In addition to binding to the receptor, the hormone must induce receptor transactivation to produce the hormonal effect. If the hormone binds to the receptor without allowing the transactivation of the DNA machinery, an antagonistic effect may be produced (Liu et al., 2002).

The progestational action of P, as well as that of the progestins, is mediated by the PR. In the target cell, P produces a dramatic change in PR conformation, which is associated with transforming the PR to an active form that can bind to specific DNA elements. This transformation is accompanied by a loss of associated heat shock proteins and dimerization. The activated PR dimer, comprised of PR-A and PR-B, then binds to specific DNA sequences within the promoter region of P-responsive genes, referred to as P-response elements (Giangrande and McDonnell, 1999). The agonist-bound PR is believed to activate transcription by associating with coactivators, which act as bridging factors between the receptor and the general transcription machinery. This is followed by increases in the rate of transcription producing agonist effects at the cellular and tissue levels (Liu et al., 2002).

**Table I. Classification of older and new progestins**

<table>
<thead>
<tr>
<th>Pregnanes</th>
<th>Estranes</th>
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<tbody>
<tr>
<td><strong>Older progestins</strong></td>
<td></td>
</tr>
<tr>
<td>Derived from progesterone</td>
<td>Derived from Testosterone (ethinylated)</td>
</tr>
<tr>
<td>Retropregesterone</td>
<td>Norethisterone (and acetate)</td>
</tr>
<tr>
<td>Derived from 17-hydroxy progesterone</td>
<td>Norethynodrel</td>
</tr>
<tr>
<td>Chlormadinone acetate</td>
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<tr>
<td>Cyproterone acetate</td>
<td></td>
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<tr>
<td>Medroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td>Derived from 19-norprogestrone</td>
<td>Gonane derivatives (less androgenic)</td>
</tr>
<tr>
<td>Demegestone</td>
<td>Desogestrel</td>
</tr>
<tr>
<td>Promegestone (R5020)</td>
<td>Ketodesogestrel→etonogestrel</td>
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<tr>
<td>Trimegestone</td>
<td>Gestrone</td>
</tr>
<tr>
<td>New progestins</td>
<td>Norgestimate→norelgestromine</td>
</tr>
<tr>
<td>19-norprogestrones</td>
<td>Non-ethinylated</td>
</tr>
<tr>
<td>Nestorone®</td>
<td>Dienogest</td>
</tr>
<tr>
<td>Nomegestrol acetate</td>
<td>Spirolactone derivative</td>
</tr>
<tr>
<td>Trimegestone</td>
<td>Drospirenone</td>
</tr>
</tbody>
</table>

**In vitro tests: binding affinity to steroid receptors**

Progestins may be compared by evaluating their relative binding affinities (RBAs) for the various steroid receptors in comparison to that of the physiological reference hormones (set at 100%). The RBAs of the new progestins for the ER, AR, MR and GR (as compared with E₂, testosterone, aldosterone, and cortisol, respectively) are summarized in Table II. The range of RBAs for the new progestins suggests that there are considerable differences in activity among these molecules. However, the binding affinity to the steroid receptors does not always correlate with the *in vivo* tests of estrogenic or androgenic potency.

In a study measuring binding to AR derived from the rat ventral prostate, the RBAs for LNG and 3-keto-DSG were 70 and 40%, respectively, as compared with 100% for T, whereas NES and P did not show significant binding to the AR (Figure 1) (Kumar et al., 2000). Although MPA is not derived from testosterone but from 17α-hydroxyprogesterone, it has an RBA for the AR of 36% (Philibert et al., 1999).

**In vivo bioassays**

Very small structural changes may account for considerable differences in the effects of progestins. Several *in vivo* bioassays conducted

| Table II. Binding of progestins with human steroid receptors in vitro |
|------------------|---|---|---|---|---|---|
| Receptor        | TMG | MPA | NETA | GES | LNG | DRSP |
| Progestrone      | 588 | 298 | 134  | 864 | 323 | 19  |
| Androgen         | 2.4 | 36  | 55   | 71  | 58  | 2   |
| Glucocorticoid   | 13  | 58  | 1.4  | 38  | 7.5 | 3   |
| Mineralocorticoid| 42  | 3.1 | 2.7  | 97  | 17  | 500 |
| Estrogen         | <0.02 | <0.02 | 0.15 | <0.02 | <0.02 | <0.5 |

DRSP, drospirenone; GES, gestodene; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; TMG, trimedostine.


**New progestins**

**DNG**

DNG is structurally related to the norethindrone family of testosterone derivatives but acts as an antiandrogen. Like the others in this family, DNG has the same 18-carbon nucleus as the estrane structure (Oettel and Holz, 2000; Teichmann, 2003). DNG differs in structure from norethindrone by having a cyanoethyl group instead of an ethinyl group at C-17 and by the addition of a double bond between C-9 and C-10 (Oettel and Holz, 2000; Teichmann, 2003). DNG has a high bioavailability (96.2%) and a rather short terminal half-life (11.6 h) (Teichmann, 2003).

The Hershberger test evaluating the antiandrogenic effect of various progestins indicates that DNG has about 40% of the potency of cyproterone acetate (CPA) the most potent antiandrogenic progestin (Elger et al., 2003).

When DNG is combined with ethinyl-estradiol (EE) (30 μg EE plus 2 mg DNG daily) (Valette®, the combination is an effective combined oral contraceptive (COC; Pearl Index ~0.2). This COC has good bleeding control and improves androgenic symptoms (Foster and Wilde, 1998; Wiegratz et al., 2002).

Wiegratz et al. (2002) studied the effect of four OCs on lipid metabolism in 100 women randomized to receive either DNG in three different formulations, or a combination of EE and LNG. The changes in lipid metabolism caused by the DNG-containing formulations appeared to be more favorable than those observed with EE/LNG due to the difference in androgenicity of the progestin.

**DRSP**

DRSP, which is derived from spirolactone, is essentially an antimineralocorticoid progestin (Oelkers et al., 1991; Pollow et al., 1992; Fuhrmann et al., 1996; Krattenmacher, 2000; Elger et al., 2003). The affinity of DRSP for the MR is about 5 times the affinity of aldosterone itself. In addition, DRSP has some antiandrogenic
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Table III. In vivo bioassays for testing progestins (Kumar et al., 2000)

<table>
<thead>
<tr>
<th>Bio activity</th>
<th>Test</th>
<th>Species</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestational</td>
<td>McPhail Index</td>
<td>Immature female rabbits</td>
<td>Endometrial transformation</td>
</tr>
<tr>
<td>Progestational</td>
<td>Pregnancy maintenance</td>
<td>Female rats</td>
<td>Dose able to maintain pregnancy after ovariectomy</td>
</tr>
<tr>
<td>Anti-ovulatory</td>
<td>Ovulation inhibition test</td>
<td>4-day cyclic rats</td>
<td>Dose able to suppress spontaneous ovulation</td>
</tr>
<tr>
<td>Androgenic</td>
<td>Hershberger assay</td>
<td>Immature or castrated male rats</td>
<td>Growth of prostate and seminal vesicles</td>
</tr>
<tr>
<td>Anti-androgenic</td>
<td>Hershberger assay</td>
<td>Immature or castrated male rats treated with T</td>
<td>Inhibition of T-induced prostate and seminal vesicles growth</td>
</tr>
<tr>
<td>Estrogenic/anti-estrogenic</td>
<td>Uterotropic/vaginal cornification</td>
<td>Immature or ovariectomized female rats</td>
<td>Uterine growth and vaginal cornification</td>
</tr>
<tr>
<td>Glucocorticoid/anti-glucocorticoid</td>
<td>Thymolytic assay and liver glycogen</td>
<td>Adrenalectomized male rats</td>
<td>Growth of thymus and liver glycogen content</td>
</tr>
<tr>
<td>Mineralocorticoid/anti-mineralocorticoid</td>
<td>Electrolyte balance and water retention</td>
<td>Adrenalectomized rats</td>
<td>Urinary Na/K</td>
</tr>
</tbody>
</table>

19-Norpregnanes

The 19-norpregesterone derivatives of P (19-norpregnanes) are referred to as ‘pure’ progestational molecules as they bind more selectively to the PR. This category includes NOMAc, an acetylated compound (Paris et al., 1983), as well as four non-acetylated molecules: demegestone, progesterone (also known as R5020), TMG (a promegestone prodrug) (Winneker et al., 2003) and NES (Kumar et al., 2000). The 19-norpregnosterones are derived from the progesterone structure but have one less carbon as they do not have a radical methyl at C-19. Although these compounds were synthesized in the early 1980s, two of the three discussed in this review are still in clinical development and may therefore be called ‘new’ progestins.

TMG

TMG differs from promegestone by the presence of a hydroxylated carbon on the penultimate carbon of the side chain (C-17). TMG is twice as potent as NES on the McPhail Index. However, on the ovulation inhibition test, TMG is closer in activity to medroxyprogesterone acetate (MPA) (Winneker et al., 2003). The activity of TMG on the rat uterine decidualization and ovulation assays is similar to MPA but the antiestrogenic activity of TMG evaluated by rat uterine complement C3 mRNA expression was five times greater than that of MPA (Lundeen et al., 2001).

The RBA of TMG for the PR is 588, indicating a high affinity for the PR but only 42 for the MR (Philibert et al., 1999). TMG has also been demonstrated to have weak antiandrogenic activity and some antimineralocorticoid activity (Zhang et al., 1999; Winneker et al., 2003).

TMG binds to the human PR with an affinity greater than do MPA, norethisterone (NET) or LNG. In contrast, TMG binds with low affinity to the AR, the GR, and the MR and has no measurable affinity for the ER. Compared to other progestins, TMG demonstrates an improved separation of its affinity for the PR from its affinities to other classical steroid hormone receptors. In vivo, TMG has potent progestin activity. For example, TMG produces glandular differentiation of the uterine endometrium in rabbits and is about 30 and 60 times more potent than MPA and NET, respectively. In the rat, TMG does not have significant androgenic,
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glucocorticoid, anti-glucocorticoid or mineralocorticoid activity but it does have antimineralocorticoid activity and modest antiandrogenic effects. The overall profile of TMG is qualitatively similar to that of P. When TMG is administered chronically, it antagonizes the effect of E₂ on the uterus but does not antagonize the beneficial bone-sparing activity of E₂ (Bouali et al., 2001).

In an experimental model of osteoporosis in ovariectomized rats, E₂, given alone, prevented further bone loss and reduced bone turnover, as measured by biochemical and histomorphometric markers. When given with E₂, TMG enhanced its beneficial effects on bone loss and bone turnover (Bouali et al., 2001).

In studies in rats, which evaluated central nervous system (CNS) gamma-aminobutyric acid (GABA) (A) receptor modulatory activity, TMG had less activity on this undesirable endpoint than did P and norethindrone acetate (NETA), which may translate into fewer mood-related side effects (Winneker et al., 2003).

Most of the clinical experience with this progestin has been collected in the treatment of postmenopausal women (Grubb et al., 2003).

In a dose-ranging study evaluating sequential combination therapy with E₂ (2 mg) plus TMG (0.05, 0.1, 0.25 or 0.5 mg), given daily, to postmenopausal women, 96% of the endometrial specimens obtained at study termination had secretory changes without hyperplasia. In addition, the progestin did not negate the beneficial effect of E on the lipid profile during treatment, a finding related to the lack of androgenic activity of TMG (Grubb et al., 2003).

Although TMG is one of the most potent progestins of the new generation, it is not presently developed as a contraceptive. Preliminary work using TMG in a transdermal system indicated the feasibility of such a delivery system (Maillard-Salin et al., 2000), but no clinical trials have been published so far.

NES

Pharmacological properties of NES

One of the most potent progestins is NES (16-methylene-17α-ace-toxy-19-norpregn-4-ene-3, 20-dione), a 19-norprogesterone derivative. NES’s 19-methyl substitution and the addition of the 16-methylene substituent, which enhances binding to the PR, contribute to the molecule’s high progestational activity (Kumar et al., 2000; Stanczyk, 2002).

NES is not active orally but is active at target tissues when administered continuously through sustained-release implants, vaginal rings or transdermal systems. This progestin has been essentially studied for contraceptive purposes.

NES, like P, does not bind to sex hormone binding globulin (SHBG) and has a shorter half-life and higher clearance rate than progestins that exhibit SHBG binding (Fotherby, 1990). The oral bioavailability of NES is only about 10%, and its half-life is shorter than that of the progestins that bind to SHBG. However, a much slower elimination rate is observed with the sustained-release subdermal NES implant (Noe et al., 1993). The lack of SHBG binding and the large volume of distribution is consistent with the high affinity of NES for PR and its accumulation in extravascular space (Noe et al., 1993). The free fraction of NES and other progestins, such as P, DRSP and DNG that do not bind to SHBG (Oettel et al., 2001), should be greater than most testosterone-derived progestins that bind to SHBG.

According to the standard in vivo bioassays, NES appears to be one of the most potent progestins with respect to progestational and antiovulatory activities. On the McPhail Index, NES exhibited 10 times greater potency than LNG and was 100 times more potent than P (Figure 2) (Kumar et al., 2000; Sitruk-Ware, 2004). NES was 100 times more potent when administered s.c. than when given orally. On the pregnancy maintenance test in ovariectomized rats, NES 0.3 mg was as effective as LNG 0.3 mg or P 5 mg in maintaining pregnancy; NES had the highest potency when the steroids were administered s.c.

Using the ovulation inhibition assay in rats with normal estrus cycles, a dose-dependent inhibition of spontaneous ovulation was observed for P, LNG and NES when administered s.c. NES was the most potent of the three, completely inhibiting ovulation at a daily dose of 10 μg versus LNG 20 μg or P 900 μg. (Kumar et al., 2000).

Using the in vivo models for the androgenicity, LNG and 3-keto-DSG are androgenic, increasing the weight of the ventral prostate in a dose-dependent manner, whereas NES and P do not induce such effects. The weights of the ventral prostate and the levator ani muscle of immature castrated male rats after NES treatment were compared to those after treatment either with testosterone, the control or with 3-keto-DSG or LNG. Both LNG and 3-keto-DSG produced a dose-dependent weight increase of the ventral prostate.

NES had no androgenic or antiandrogenic activity when administered at a dose of 20 mg·kg⁻¹·day⁻¹, which far exceeds the effective dose for contraception in humans. Estrogenicity, measured by the increase in uterine weight, was significantly increased by LNG but not by NES at similar doses. Neither progestin was shown to bind to the ER (Kumar et al., 2000).

Kumar et al. (2003) using the rat uterine complement C3 expression as a model showed that the antiestrogenic activity of NES was superior to that of DSG or LNG.

The glucocorticoid activity of progestins may account for some of their unwanted effects. MPA, GES and NES have been shown to bind to the GR. Although MPA had glucocorticoid-like effects at high doses and stimulated tyrosine aminotransferase (TAT) activity (Guthrie and John, 1980), NES, even at high doses, did not show glucocorticoid activity in the in vivo assays in which

![Figure 2. Progestogenic and antiovulatory potencies of the new progestins.](http://humupd.oxfordjournals.org/)

[From Sitruk-Ware (2004) Drugs Aging 21,865–883.]
increases in liver glycogen and TAT were measured. However, when given in doses 2000 times higher than the dose required to block ovulation in ovariectomized female rats, NES caused thymus regression (Kumar et al., 2000).

**NES applications in contraceptive delivery systems**

**Vaginal delivery of NES.** A NES-only vaginal ring is being developed as a contraceptive based on the potent antiovulatory effect of this progestin. In a 6-month study of continuous use in 180 women, vaginal rings delivering 50, 75 or 100 μg per day were evaluated (Brache et al., 2001) NES serum levels remained fairly constant throughout the study at 125, 200 and 250 pmol/l for the low-, mid- and high-dose groups, respectively. Luteal activity was not dose-related and occurred infrequently (in 1.2 to 2.6% of sampling periods). With the two higher doses, the inhibition of follicular maturation was more pronounced; E2 levels remained in the range of 300–400 pmol/l, which is compatible with early follicular phase E levels. All three doses effectively inhibited ovulation, and luteal activity was suppressed when NES serum levels were >100 pmol/l. These results indicate the excellent antigonadotropic effect of NES; NES doses as low as 75 μg/day were sufficient to suppress ovulation effectively and to prevent follicular growth. When associated with EE in a 1-year contraceptive vaginal ring, the combination of 150 μg/day of NES and 15 μg/d of EE showed a high efficacy on ovulation suppression in a phase 2 study (Sivin et al., 2005). The project is now entering into phase III.

**Subcutaneous delivery of NES via implants.** A single implant-releasing NES alone has been tested in lactating women in a 2-year study comparing the NES implant to the Copper T intrauterine device (T-Cu) (Massai et al., 2001). NES is inactive orally and thus will not affect the nursing infant. The implant, which is 4 cm in length and has a silicone drug matrix core containing 80 mg of NES, initially releases, in vitro, about 100 μg per day. The mean NES serum levels were 175 pmol/l at one month post-insertion; by the end of the first year, NES levels had decreased to 60 pmol/l. No pregnancies occurred in 2195 and 2145 women-months of exposure to the NES implant and the T-Cu, respectively. During lactation and in the first 6 months of the study, NES implant users had significantly less irregular bleeding than did the T-Cu users (P < 0.002). Implant users exhibited significant increase in irregular bleeding after infant weaning (P < 0.05), similar to that experienced by T-Cu users. No serious adverse events that were likely to be related to NES implant use were observed in either group. A phase III should start once the laboratory-scale prototype implants have been up-scaled in a certified manufacturing site.

**Transdermal delivery systems for NES.** Although inactive orally, NES is particularly well suited for transdermal delivery because it is highly active when applied to the skin and achieves good systemic bioavailability. Preliminary results of clinical trials of a NES gel indicate that NES is absorbed transdermally and, due to its high prostaglandin potency and anti-ovulatory effects, can achieve systemic serum levels that suppress ovulation in most of the subjects (Croxatto and Zepeda, 1992; Sitruk-Ware et al., 2003). In a 3-month multicenter phase IIa study of 150 normal cycling women, NES gel was applied to abdominal skin in daily doses of 0.3, 0.6 and 1.2 mg. Results showed a clear dose-response effect in serum NES levels achieved and in ovulation inhibition: 53, 64 and 83%, respectively. (Population Council, unpublished data). Formulation optimization is ongoing with a higher concentration of the steroid for further development.

Given its pharmacologic profile, the safety and efficacy of NES delivered transdermally with or without E deserves further research. Studies are ongoing with gels with NES alone or combined with E2 as well as a metered-dose transdermal system (MTDS) that delivers an invisible film on the skin leading to a stable release of NES over 24 h (La Guardia et al., 2004).

Among the progestins tested for transdermal hormone therapy, NES and TMG are the most suitable compounds; they rate among the most potent prostaglandin molecules and have proved to be active at very low doses.

**NOMAc.** NOMAc is formed by adding a double bond between C-6 and C-7 of the hydroxyprogesterone skeleton and deleting the CH3 radical at C-19. These structural changes confer a higher progestational potency to NOMAc than to MPA (Paris et al., 1983; Kuhl, 1996a).

In experiments testing the effects of progestins on the prostate growth, Duc et al. (1995) showed no effect of NOMAc even when administered at very high doses. NOMAc has a partial antiandrographic effect, which is 20 times lower than that of CPA. In similar experiments, NOMAc had no androgenic effect (Duc et al., 1995). Bazin et al. (1987) showed that oral NOMAc at a dose of 1.25mg per day inhibited ovulation while permitting follicle growth, while doses of 2.5 or 5mg per day suppressed both ovulation and follicle development. Lower doses of NOMAc were used in contraceptive implants and were showing efficacy in preventing pregnancy with one implant used over 1 year (Coutinho, 1993; Devoto et al., 1997). New studies will be started with this compound combined with E2 to develop an OC as announced by Organon who recently acquired the product (Organon Press release May 31, 2005).

**Side effects and risks of progestins used in contraception**

**Side effects**

Most of the side effects attributed to progestins are usually related to the effects of combined E-progestin products or of high doses of the older molecules such as depot medroxyprogesterone acetate (DMPA) or LNG and NET. The effects vary whether the progestin is associated with E or not, and when the progestin is used alone, whether the dose is blocking or not the follicular maturation and the endogenous production of E2. In addition, the side effects may be related either to the androgenic or to the glucocorticoid properties of a progestin or to its estrogenic effects (Sitruk-Ware, 2000). These adverse events are usually reported as headaches, bloating, mastalgia, weight gain, mood changes and acne, in addition to bleeding problems (Nelson, 1996; Erkkola and Landgren, 2005). Not all of side effects occur with all of the progestins. Acne is usually observed when androgenic molecules are used such as LNG at high doses and headaches are more often observed either due to hypotrogenism in women receiving high doses of antagonotropic agents or due to hyperestrogenism in combinations where the E is predominant. Bloating and weight gain are more usually observed with molecules such as MPA, which at high doses exert glucocorticoid-like activity, leading to salt and water retention. In addition, androgenic progestins are stimulating insulin secretion (Wynn et al., 1979), which may be responsible for true weight
gain. In contrast, the new molecules, which are devoid of androgenic effect or exert anti-androgenic action, may rather treat acne. Decrease in libido may theoretically be attributed to antiandrogenic molecules but this symptom has rarely been reported with the low doses used in contraceptives. (Schneider, 2003) Antimineralocorticoid molecules such as DRS was rather induce salt and water elimination and prevent the small weight gain associated with water retention (Oelkers et al., 1995).

**Progestins and venous risk**

The major risks attributed to hormonal contraceptives have been focused on the risk of venous thromboembolism (VTE) and cardiovascular disease although the occurrence of such events is very rare in the young population of women using contraceptives.

The increased risk of VTE with use of OCs is well known. In all large studies conducted since 1995, the odds ratio (OR) of VTE is about four for any OC use (Farley et al., 1999). In the early 1990s, the risk of VTE was associated with the dose of EE. The VTE risk for use of an OC with a third-generation progestin was found to be about twice that for use of an OC with second-generation progestins. In a recent meta-analysis (Kemmeren et al., 2001), a relative risk of VTE of 1.7 was established for use of OCs with third-generation progestins versus second-generation progestins. The difference of effects observed between second and third generation OC may be related for some of the variables to the difference in the androgenic properties of the progestin. Third-generation progestins are less androgenic than second-generation compounds, and this difference is reflected on the changes in SHBG and HDL (Odlind et al., 2002).

Although there is no marker for VTE risk, epidemiological studies document that second-generation OCs carry lower risks than do third generation OCs. SHBG has been proposed as a possible marker of the venous risk (Odlind et al., 2002). The authors correlated the percentage of increase in SHBG with the observational data on VTE published for various categories of OCs, the higher the estrogenicity as indicated by SHBG levels, the higher the risk of VTE. However, the observational data cannot be used to extrapolate changes from a given protein as a surrogate marker to the risk of VTE.

OCs containing EE generally increase the synthesis of SHBG, but the progestogen component modifies this effect (Odlind et al., 2002). An OC containing the androgenic progestogen LNG is not associated with a high increase in SHBG, while other progestagens, such as DSG, GES (GES), or CPA, which are less androgenic or antiandrogenic, are associated with a higher SHBG increase as they do not oppose the estrogenic effect. The dose of EE influences the rise in SHBG, but the progestogen component modulates the dose response.

In the EURAS post-marketing surveillance study (Heinemann and Dinger, 2004) comparing a new OC containing an antiandrogenic progestin, DRS, which does not oppose the EE-related increase in SHBG, with other second or third generation of OCs on the incidence of VTE no differences in relative risk of VTE were observed. This observation is of interest as the magnitude of changes in SHBG was significantly different between the new OC and a LNG containing OC.

EE impacts strongly on the liver proteins whether delivered parenterally or orally. The assumption that non-oral delivery would avoid the first pass effect on the liver appears to be true for E2 but not for EE, which has a long half-life and is not metabolized readily (Goebelsmann et al., 1985). It has been previously shown that EE given vaginally would stimulate corticosteroid-binding globulin (CBG) and SHBG as well as oral EE (Goebelsmann et al., 1985). Therefore, the same cautions and contraindications that apply to OCs are likely to apply to any system containing EE and new progestins with non-androgenic properties would not oppose this effect of EE.

The influence of progestins on hemostasis parameters depends on type and dose of the association with that of an E, the route of administration and the duration of its application (Kuhl, 1996b). When used with ethinyl estradiol (EE), several combinations of E and progestins lead to an acceleration of coagulation and fibrinolysis (Wiegart et al., 2004). This is primarily induced by the hepatic impact of EE. Wiegart et al. (2004) showed an antagonistic effect of LNG on the EE-induced rise on some coagulation and inflammation markers such as factor VII activity and fragment 1 + 2 and on the EE-dependent reduction of total and free protein S but not with DNG, an antiandrogenic progestogen. Therefore, progestogens with androgenic properties may counteract the E-induced changes in the hepatic synthesis of platelet aggregation and readiness for coagulation while non-androgenic progestins would not (Kuhl, 1996a; Wiegart et al., 2004; Rad et al., 2005).

Progestogen-only pills cause only minor effects on coagulation and fibrinolysis (Kuhl, 1996b). In combinations of EE and new progestins, the studies of clotting factors and liver proteins show a profile similar to the third-generation contraceptives (Magnusdottir et al., 2004; Rad et al., 2005).

Very few epidemiological studies have considered the risk of progestins given alone for contraception, without E. In a retrospective case-control study, Conard et al. (2004) studied women at high risk of VTE who received CMA for contraceptive purpose (CMA is a pregnane derivative from the second-generation of progestins). They found no increase in risk in CMA users as compared to controls with a relative risk of VTE at 0.8 (95% confidence interval = 0.2–3.9). Further studies with the new progestins used alone are warranted.

With associations of new progestins and E2, the effect on clotting factors should theoretically be neutral, but data has yet to come. The future should bring new combinations of hormonal contraceptives using E2 instead of EE and the use of non-androgenic progestins with potent antigonadotropic properties will ensure the contraceptive effect with a better tolerability profile and less impact on the liver metabolism than with EE.

**Progestins and the breast**

The role of progestins on the breast cells has been controversial since the past three decades. The action of the progestins on the breast cells differ according to the molecule, dose and duration of use and the resulting balance between cell proliferation and apoptosis (Desreux et al., 2003; Sitruk-Ware and Plu-Bureau, 2004). However, progestins are usually combined with EE in hormonal contraceptives and the final results depend on the balance of effects on the breast tissue.

It has been demonstrated that breast cells in the late phase of cell cycle activity are initially driven to the S phase of DNA synthesis by progestins (Musgrove et al., 1991). This effect is transient
and further application of progestins suppresses the cyclins, halting breast cell division in early G1 phase. In addition, the normal cell cycle in breast cells can be shifted from cell division to cell differentiation under the action of P as has been shown in a study with MCF-7 human breast cells in which progesterin-induced growth inhibition was due to cell differentiation rather than to apoptosis (Alkhalaf et al., 2002).

In a recent study conducted in surgically postmenopausal cynomolgus monkeys conjugated equine estrogen (CEE) plus MPA induced a diffuse epithelial proliferation in the mammary glands but EE plus NETA did not (Suparto et al., 2003). In another study using fine needle biopsy specimens from mammary glands of women using E2 (2 mg) or estradiol valerate (EV) 2 mg plus NETA (1 mg) or DNG (2 mg), (Conner et al., 2003) Ki67, used as a proliferation marker, did not differ significantly between NETA or DNG although the DNG group showed a tendency for a weaker proliferation.

In addition, previous in vitro studies in MCF-7 or T47D breast cell lines have compared the effects of several progestins on cell proliferation (Catherino et al., 1993; Catherino and Jordan, 1995). In these studies, NORMAc, as well as MPA, did not induce proliferation while GES and LNG did promote proliferation. Whether the in vitro data can be extrapolated to a clinical setting has long been debated. Only a long-term randomized controlled trial could provide definite proof that various progestins act differently on the risk of breast cancer. However, using the available tools, under the same experimental conditions, not all progestins have the same effects on breast cells.

Epidemiological studies have raised controversies as to the role of progestins used in HRT for the risk of breast cancer (Million Women Study collaborators, 2003; Sitruk-Ware and Plu-Bureau, 2004; Dietel et al., 2005). The Million Women study suggested that users of several of the older progestins used in HRT would increase the risk of breast cancer within the first 2 years of treatment. One of the most recent observational studies showed differences in risk according to the categories of progestins used in HRT and no risk was found for users of natural progesterone (Fournier et al., 2005). Dietel et al. (2005) studying the pathological aspect of hormone-sensitive breast cancers indicated that the long developmental process of tumors is in apparent contradiction to results of some epidemiological studies that showed increased cancer risk, implying primary initiation in HRT users within observation periods of 1–6 years. This indicates that great caution should be exercised when interpreting epidemiological studies. Whether the use of hormonal contraceptives increases the risk of breast cancer later in life, when the incidence of breast cancer is increased has been largely studied. In the most recent population-based, case–control study, current or former oral-contraceptive use was not associated with a significantly increased risk of breast cancer (Marchbanks et al., 2002). The role of new combinations is still unknown and further studies are warranted.

Conclusion

In conclusion, the progestins available for contraception are not similar. There may be profound differences among these molecules according to their structure, metabolites and pharmacodynamic actions. It is therefore inappropriate to consider the various effects of the older and newer progestins as class effects.

The new progestins developed for contraceptives and HRT regimens have been designed to be closer in structure and function to the natural hormone P. Their design suggests that their use should not be accompanied by adverse effects on the surrogate markers of cardiovascular risk. Preliminary data on the new progestins from pharmacologic studies supports the potential of these agents to be generally well tolerated, but their final effect will depend upon the type and dose of the associated estrogen.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The author thanks Barbara Tokay for her professional assistance in preparing the manuscript and Amparo Solari for editorial help. NES, a progestin mentioned in this review, was developed by the Population Council; development of NES for contraceptive use was funded by grants from the United States Agency for International Development and the National Institute of Child Health and Development. The views of the author do not necessarily reflect those of the Population Council or the funding agencies.

References


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Submitted on July 11, 2005; resubmitted on September 11, 2005; accepted on September 29, 2005