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Pharmacokinetics, metabolism and serum concentrations of progestins used in contraception

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Abstract

Many different forms of hormonal contraception are used by millions of women worldwide. These contraceptives differ in the dose and type of synthetic progestogenic compound (progestin) used, as well as the route of administration and whether or not they contain estrogenic compounds. There is an increasing awareness that different forms of contraception and different progestins have different side-effect profiles, in particular their cardiovascular effects, effects on reproductive cancers and susceptibility to infectious diseases. There is a need to develop new methods to suit different needs and with minimal risks, especially in under-resourced areas. This requires a better understanding of the pharmacokinetics, metabolism, serum and tissue concentrations of progestins used in contraception as well as the biological activities of progestins and their metabolites via steroid receptors. Here we review the current knowledge on these topics and identify the research gaps. We show that there is a paucity of research on most of these topics for most progestins. We find that major impediments to clear conclusions on these topics include a lack of standardized methodologies, comparisons between non-parallel clinical studies and variability of data on serum concentrations between and within studies. The latter is most likely due, at least in part, to differences in intrinsic characteristics of participants. The review highlights the importance of insight on these topics in order to provide the best contraceptive options to women with minimal risks.

Keywords

Progestin; pharmacokinetics; metabolism; serum concentration; contraception

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1. Introduction

A range of progestins, or synthetic progestogens, is used at different doses in various formulations for endocrine therapy in women (Africander, et al., 2011; Sitruk-Ware, 2004; Sitruk-Ware, et al., 2013), such as menopausal hormonal therapy (MHT) and contraception. Progestins include compounds structurally related to progesterone (P_4) or testosterone (Stanczyk, et al., 2013). Although they all have progestational activity, they exhibit a wide range of other properties which can translate into different clinical outcomes and thus cannot be considered as a single class of compound. These differences most likely arise due to different off-target effects via various steroid receptors (SRs) and other steroid-binding proteins, as well as differences in metabolism, pharmacokinetics and pharmacodynamics (Africander, et al., 2011; Hapgood, et al., 2018; Stanczyk, et al., 2013). We will focus on hormonal contraceptives (HCs), although many of the topics are also relevant to MHT. Side-effects of HCs may include effects on susceptibility to infectious diseases, immune function, breast cancer and cardiovascular disease (reviewed in (Africander, et al., 2011; Hapgood, et al., 2018; Marjoribanks, et al., 2017; Stanczyk, et al., 2013)). Increasing interest in these issues, coupled with improved technology and a drive to use lower doses of progestins (Polis, et al., 2018; Shelton & Halpern, 2014) and determine minimum doses for contraceptive efficacy (Callahan, et al., 2015; Cherala, et al., 2016), have led to several new insights on progestin pharmacokinetics and techniques to measure progestins in serum and genital tract samples from women on contraceptives (Blue, et al., 2018; Buckner, et al., 2019; Laszlo, et al., 2019). Issues such as objective measures of contraceptive usage rather than relying on self-reporting by trial participants are becoming crucial to interpretation of clinical trial data (Achilles, Mhlanga, et al., 2018; Heffron, et al., 2017). It is evident that there may be a high degree of inter-individual variability in progestin serum concentrations between women that may depend on multiple intrinsic factors, making determination of *in vivo* progestin concentrations important. Requirements for access to more diverse contraceptive choices (WHO, 2019) and increased use of HCs together with anti-retroviral (ARV) drugs has increased interest in progestin pharmacokinetics and drug-drug interactions (Achilles, Hendrix, et al., 2018; Chappell, et al., 2017; Cohn, et al., 2007; Heffron, et al., 2014; McNicholas, et al., 2015; Mornar, et al., 2012; Nanda, et al., 2016; Sierra-Ramirez, et al., 2011; Thurman, et al., 2013; Thurman, et al., 2018; Zia, et al., 2019). Here we review the pharmacokinetics, metabolism and serum concentrations of progestins with a focus on those most widely used in HCs worldwide and in sub-Saharan Africa.

2. Commonly used methods of HC

HCs vary in the type and dose of progestin, absence or presence of an estrogenic compound, as well as the method and frequency of administration (Sitruk-Ware, et al., 2013). In low- and middle-income countries, the most common form of contraception is progestin-only injectables (United Nations Department of Economic and Social Affairs Population Division, 2015, 2019), which are highly effective, reversible methods. The most common form is the three-monthly intramuscular (IM) injection of 150 mg of medroxyprogesterone acetate (MPA) Depo-Provera or DMPA-IM), while Sayana Press (DMPA-SQ or DMPA-SC), a three-monthly, lower (104 mg) DMPA dose injectable contraceptive delivered subcutaneously (SC) has also been introduced (Family Planning 2020 (FP2020), 2014;

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PATH, 2017; Polis, et al., 2018; Schivone, et al., 2016). Another progestin-only injectable widely used in South Africa is Nur-Isterate or Norigest, a two-monthly injection containing 200 mg of norethisterone (NET) enanthate (NET-EN) (Heffron, et al., 2019; National Department of Health & ICF, 2019). Other long-term highly efficient and reversible progestin-only contraception methods include etonogestrel (ETG)-releasing subdermal implants (Implanon, Nexplanon) and intravaginal rings (IVRs) (NuvaRing), as well as levonorgestrel (LNG)-releasing implants (Jadelle, Norplant, Sino-Implant) and intra-uterine devices (IUDs) (Mirena, Skyla, Liletta) (Sitruk-Ware, et al., 2013). LNG is used extensively worldwide in many different HCs (Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium, 2019; Polis, Phillips, et al., 2016; United Nations Department of Economic and Social Affairs Population Division, 2015, 2019). Less widely used progestin-only contraceptives include administration of nestorone (NES) in an IVR or implant (Sitruk-Ware, et al., 2003). Most estrogen-containing contraceptives are administered as combined oral contraceptives (COCs), which currently contain varying doses of the progestins nomegestrol acetate (NoMAc), drospirenone (DRSP), gestodene (GES), dienogest (DNG), norgestimate (NGM), cyproterone acetate (CPA), LNG, ETG or NET (Sitruk-Ware, et al., 2013). Some estrogen-containing contraceptives are administered by other routes, such as IM injection of MPA plus estradiol (E_2) cypionate (E_2C) (Cycloprovera, Cyclofem or Lunelle) (Kaunitz, 2001) or IVRs containing NES, ETG or NET (Sitruk-Ware, et al., 2013) or a transdermal patch containing norelgestromin (NGMN) (Abrams, et al., 2002), which all also contain ethinyl estradiol (EE). Besides the abovementioned progestins, there are several others, which will not be discussed in this review since there is very little information available and they are not widely used.

3. Progestins and SRs

Progestins exert their biological effects via binding to and activating intracellular SRs, which are ligand-activated transcription factors that regulate transcription of specific target genes by multiple mechanisms (Jacobsen & Horwitz, 2012; Newton, et al., 2010; Oakley & Cidlowski, 2013; Scheschowitsch, et al., 2017). The progestogenic activity of all progestins is due to their actions via the progesterone receptor (PR) (Enfield, et al., 2020). However, some progestins also bind to and activate other members of the SR family to different degrees, including the classical glucocorticoid, androgen and mineralocorticoid receptors (GR, AR and MR, respectively), exerting differential agonist, partial agonist or even antagonistic transcriptional effects via some of these receptors (Africander, et al., 2013; Koubovec, et al., 2005; Louw-du Toit, et al., 2020; Louw-du Toit, et al., 2017; Ronacher, et al., 2009). We have previously comprehensively reviewed the mechanisms of action of progestins via SRs (Africander, et al., 2011; Hapgood, et al., 2014; Hapgood, et al., 2018; Hapgood, et al., 2004).

Established and potential differential actions of progestins via SRs most likely form the basis for their differential clinical outcomes and side-effects, besides differential actions due to pharmacokinetics and metabolism. Of particular interest are the pharmacokinetics and side-effects of DMPA-IM compared to DMPA-SC and intramuscular NET-EN, since DMPA-IM has been associated with increased HIV-1 acquisition compared to NET-EN and condom use or no contraception, although the observational data have limitations (Morrison,

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et al., 2015; Polis, Curtis, et al., 2016; Ralph, et al., 2015). No such increased risk of HIV-1 acquisition has been detected for COCs, while little information is available for other HCs. Data from a recent randomized open-label trial suggest that DMPA-IM has a 23-29% increased risk, but has less than a 50% increased HIV-1 risk, compared to an LNG implant (Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium, 2019). Notably, MPA, unlike NET and LNG, binds the GR with a relatively high affinity (Hapgood, et al., 2018; Koubovec, et al., 2005; Ronacher, et al., 2009; unpublished data). Although several progestins are discussed in this review, most available data on pharmacokinetics, metabolism and serum concentrations reviewed here are for MPA, NET and LNG.

4. Pharmacokinetics and metabolism of progestins

The concentration of the progestin available to elicit biological actions in target tissues is influenced by factors such as route of administration, metabolism, bioavailability, half-life and availability after binding to steroid-binding proteins. Here, we discuss these factors for select progestins used in contraception (Fig. 1).

4.1. Route of administration and metabolism

Information on the metabolism of progestins in humans is scant; however, available studies suggest that this is influenced by route of administration i.e. oral or parenteral (IM injections, implants, vaginal gels or rings, IUDs and transdermal patches) (Africander, et al., 2011; Stanczyk, et al., 2013). In contrast to parenterally administered progestins, progestins taken orally undergo hepatic first-pass metabolism, resulting in a significant reduction in progestin concentration (Stanczyk, et al., 2013). Hepatic first-pass progestin metabolism occurs via steroidogenic enzymes like cytochrome P450 enzymes, hydroxysteroid dehydrogenases (HSDs) and reductases in the intestinal mucosa. Subsequently, progestin metabolites and unmetabolized progestins are transported via the portal vein to the liver, where several metabolites, many of which remain unidentified, are produced by steroidogenic enzymes (Edelman, et al., 2010; Stanczyk, et al., 2013). The parent progestin and/or its metabolites, either unconjugated or conjugated, are then released into the blood. While unconjugated compounds are transported to target tissues, conjugated compounds are excreted in the urine and faeces. Conjugated products are formed when the hydroxyl group of the parent progestin and/or progestin metabolites is sulfated or glucuronidated (Stanczyk, 2003; Stanczyk, et al., 2013). These reactions assist with either the transport of compounds by making hydrophobic compounds more water soluble or by inactivating toxic compounds (Schonborn, 2010; Vīna, et al., 2013). Parenterally administered progestins are also significantly metabolized in the liver (Stanczyk, 2003; Stanczyk, et al., 2013). Metabolism may also occur at the site of administration or the target sites expressing steroid-metabolizing enzymes. For example, steroid 5α-reductase and 17β-HSD are not only found in the liver (Jin & Penning, 2001; Narasaka, et al., 2000) but also in the female genital tract (FGT) (endometrium (Dassen, et al., 2007; Konings, et al., 2018), vagina (Berman, et al., 2003), uterus (Konings, et al., 2018) and skin (Cassidenti, et al., 1991; Martel, et al., 1992)).

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4.2. P_4 and progestin metabolites

Progestins are used instead of P_4 in endocrine therapy due to the rapid metabolism of P_4 (Hapgood, et al., 2004; Speroff & Darney, 1996; Stanczyk, et al., 2013). Understanding the metabolism of progestogens is important as tissue- and cell-specific metabolites may result in differential beneficial and/or detrimental biological effects. We summarize below the main metabolites identified for P_4 and progestins commonly used in contraception (Fig. 1).

4.2.1 P_4—P_4 metabolism targets the 3-keto and 20-keto groups and the double-bond between carbon 4 and 5 in the A-ring of the steroid structure (Fig. 1) (Kuhl, 2011). A number of enzymes, including reductases, HSDs and cytochrome P450 enzymes have been implicated (Lewis, et al., 2004; Miller & Auchus, 2011; Wiebe, 2006). For example, in human breast tissue, P_4 is converted mainly to 4-pregnenes e.g. 3α-dihydroprogesterone, by 3α-hydroxysteroid oxidoreductase (3α-HSO) or 20S-hydroxyprogesterone by 20α-HSO, or to 5α-pregnanes (e.g. 5α-dihydroprogesterone) by 5α-reductase (Wiebe, 2006). Normal breast tissue produces significantly more 4-pregnenes than 5α-pregnanes, while in tumorous breast tissue the production of 5α-reduced metabolites is favoured (Wiebe, 2006; Wiebe, et al., 2000). While the ratio between these P_4 metabolites has been suggested to contribute to breast cancer risk (Wiebe, 2006; Wiebe, et al., 2000), a recent study did not show increased risk with the circulating ratio of the 5α-dihydroprogesterone:3α-dihydroprogesterone in postmenopausal women (Trabert, et al., 2020). Both 5α-pregnanes and 5β-pregnanes also occur in the human liver (Jin, et al., 2011; Stanczyk, et al., 2013), while hydroxylated derivatives of P_4 are produced in the human brain by cytochrome P450 CYP2D6 (Hiroi, et al., 2001). The precise functions of many of these metabolites are still unknown.

4.2.2. MPA—Although MPA has been used for more than 60 years (Regidor, 2018), information regarding its metabolism is scarce. It has been suggested that the acetate at carbon 21 may limit metabolism (Stanczyk, et al., 2013). Nonetheless, MPA can be hydroxylated at carbons 2, 6 and 21 in humans, with 6β, 21-dihydroxy-MPA (Table 1) being the major metabolite (Fukushima, et al., 1979; Helmreich & Huseby, 1962; Sturm, et al., 1991). Cytochrome P450 3A polypeptide 4 (CYP3A4), highly expressed in the liver (Lynch & Price, 2007; Thummel, 2007), may be involved in this hydroxylation (Kobayashi, et al., 2000; Zhang, et al., 2008). Although MPA itself is likely the active progestogenic compound (Hapgood, et al., 2004), further research is necessary to identify other possible metabolites, their concentrations and possible physiological functions, since MPA is the progestin associated with the most side-effects.

4.2.3. NET—NET-A and NET-EN are metabolized to the progestogenic compound NET. In the liver, NET undergoes extensive metabolism in its A-ring structure when given orally, producing dihydro- (5α-NET and 5β-NET) and tetrahydro- (3α,5α-NET, 3β,5α-NET, 3α,5β-NET and 3β,5β-NET) metabolites (Fig. 2, Table 1). The dihydro-metabolites are formed after reduction of the double bond between carbon 4 and 5 in the A-ring and after addition of hydrogen to both carbons, while the addition of a hydroxyl group to carbon 3 results in the formation of the tetrahydro-metabolites (Edelman, et al., 2010). The major metabolite in serum of women receiving 2 mg NET is 3α,5α-NET sulfate, while lower concentrations of 3α,5β-NET sulfate and 3β,5β-NET sulfate are also present (Stanczyk &

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Roy, 1990). In contrast, 3α,5β-NET sulfate is the major metabolite in women receiving 25 mg NET, while lower concentrations of 3α,5α-NET sulfate and glucuronidated 3α,5β-NET are also present (Stanczyk & Roy, 1990). Notably, high concentrations of unmetabolized NET are still present in the serum of women receiving either dosage (Stanczyk & Roy, 1990). The predominant metabolites in urine of women receiving 25 mg NET are 3α,5β-NET sulfate and 3α,5β-NET glucuronide. Metabolism of NET to the 5α-reduced metabolites 5α-NET, 3α, 5α-NET and 3β, 5α-NET by 3β-HSD and/or 5α-reductase occurs in the uterus, vagina and aorta of rats (Blom, et al., 2001). These metabolites are likely also produced in women using NET, as 3β-HSD and/or 5α-reductase are expressed in the these and other human FGT tissues (Andersson, et al., 2008; Berman, et al., 2003; Gibson, et al., 2013; Konings, et al., 2018).

NET and its acetate form, NET-A, can also be converted to the potent estrogen EE when taken orally by women (Chu, et al., 2007; Kuhnz, et al., 1997). While some studies suggest that this conversion is catalyzed by cytochrome P450 aromatase (CYP19A1) (Barbieri, et al., 1983; Yamamoto, et al., 1986), others suggest that other enzymes are involved (Kuhl, 2005; Kuhl & Wiegratz, 2007). EE displays estrogenic activity via both ER subtypes (Perkins, et al., 2017), while 5α-NET, 3α,5α-NET and 3β,5α-NET only display estrogenic activity via ER-α (Larrea, et al., 2001). Although 5α-NET is also an AR and PR agonist, it is more potent than NET via the AR, but less potent than NET via PR-A and PR-B, (Garcia-Becerra, et al., 2004; Larrea, et al., 2001). Interestingly, 5α-NET is more potent via PR-A than PR-B, while 3α,5α-NET is a partial agonist for PR-B but not PR-A (Larrea, et al., 2001).

4.2.4. NGM, NGMN and LNG—NGM is metabolized to LNG-17-acetate and NGMN, also known as 17-deacetyl-noregestimate or LNG-3-oxime (Juchem, et al., 1993; McGuire, et al., 1990), with NGMN being the main progestogenic metabolite (Fig. 2, Table 1). Both NGM and NGMN elicit progestogenic and androgenic activity (Juchem, et al., 1993; Phillips, et al., 1990; Prifti, et al., 2004). In the human liver, NGMN undergoes metabolism to form LNG (Fig. 2).

LNG is reduced to form dihydro- (5α-LNG and 5β-LNG) and tetrahydro- (3α,5α-LNG, 3β,5α-LNG, 3α,5β-LNG and 3β,5β-LNG) metabolites (Fig. 2, Table 1). However, hydroxylated metabolites of LNG, e.g. 2α-hydroxy-LNG, 16α-hydroxy-LNG, 16β-hydroxy-LNG and 16β-hydroxy-3α,5β-tetrahydro-LNG are also detected (Stanczyk & Roy, 1990). Only one study appears to have determined the concentration of LNG metabolites in serum and urine (Stanczyk & Roy, 1990). It showed that LNG is still present in its unmetabolized form in serum following an oral dose of 1.5 mg, while sulfated-, glucuronidated- and unconjugated 3α,5β-LNG metabolites are also present. Although glucuronidated 3α,5β-LNG is the major metabolite in urine, some sulfated 3α,5β-LNG and glucuronidated 16β-hydroxy-3α,5β-tetrahydro-LNG also occur. Both 3α,5β-LNG and 3α,5α-LNG are present in the serum of women (Jadelle® (LNG-releasing implant) and Mirena® (LNG-releasing IUD package leaflets) (Bayer Healthcare Pharmaceuticals Inc, 2014, 2016). These metabolites display similar, but significantly lower potencies than 5α-LNG and LNG for PR-A and PR-B, while 3β,5α-LNG is estrogenic via ERα, but not ERβ (Garcia-Becerra, et al., 2002). Although 5α-LNG, like LNG, activates both the PR and AR,

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5α-LNG is equipotent to LNG via the AR (Garcia-Becerra, et al., 2004), but less potent than LNG via the PR.

4.2.5 GES—Similar to LNG, dihydro- (5α-GES), tetrahydro- (3α,5α-GES, 3β,5α-GES) and hydroxylated metabolites of GES (1β-hydroxy-GES, 6α-hydroxy-GES, 11α-hydroxy-GES and 11β-hydroxy-GES) have been identified (Fig. 2, Table 1). GES hydroxylation in the human liver is reportedly catalysed by CYP3A4 (Ward & Back, 1993). GES, 5α-GES, 3α,5α-GES and 3β,5α-GES all display agonist activity via both PR isoforms (Garcia-Becerra, et al., 2004; Larrea, et al., 2001); however, GES is more potent. In contrast, GES and 5α-GES display similar potencies via the AR (Garcia-Becerra, et al., 2004), while the androgenic properties of 3α,5α-GES and 3β,5α-GES remain unknown. While neither GES nor its metabolites display activity via ERβ, both 5α-GES, 3α,5α-GES and 3β,5α-GES, unlike GES, display estrogenic properties via ERα (Larrea, et al., 2001).

4.2.6. ETG—ETG, also referred to as 3-keto-desogestrel, is the main progestogenic metabolite of the orally-administered progestin desogestrel (DSG) (Stanczyk, 2003; Verhoeven, et al., 1998; Viinikka, et al., 1976), and elicits stronger progestogenic activity than DSG itself (Viinikka, et al., 1976). CYP3A4 has been implicated in the metabolism of ETG to form hydroxylated metabolites in humans (Gentile, et al., 1998; Korhonen, et al., 2005) (Table 1). However, ETG is shown to be metabolized by fungi to form 6β-hydroxy-11,22-epoxy-ETG, 10β-hydroxy-ETG, 14α-hydroxy-ETG, 11,22-epoxy-ETG and 6β-hydroxy-ETG (Baydoun, et al., 2016). The latter two metabolites can inhibit the activity of β-glucuronidase (Naz, et al., 2013). Whether any of these metabolites are produced in humans, and have physiological relevance, remains to be determined.

4.2.7. NES—NES is biologically inactive when taken orally due to its rapid metabolism in the liver (Heikinheimo, et al., 1994; Kumar, et al., 2000; Noe, et al., 1993; Schindler, et al., 2008; Sitruk-Ware, 2006). Although it appears that NES metabolites have not been identified in humans, some have been identified in rodents following subcutaneous injection (Kumar, et al., 2017; Prasad, et al., 2010). One study identified 17α-deacetyl-NES and 4,5-dihydro-17α-deacetyl-NES (Prasad, et al., 2010) in serum and urine (Table 1), while another identified 5α-dihydronestorone (5α-DHNES), 20α-dihydronestorone (20α-DHNES), 3α, 5α-tetrahydronestorone (3α, 5α-THNES) and 3β, 5α-tetrahydronestorone (3β, 5α-THNES) in serum and the brain (Kumar, et al., 2017). Both 5α-DHNES and 3α, 5α-THNES display weaker progestogenic potencies than NES, while the activity of the other metabolites is not known.

4.2.8 DRSP—DRSP likely undergoes extensive metabolism, as very low levels of DRSP are observed in human urine and faeces (Wiesinger, et al., 2015), and 20 minor, inactive metabolites of DRSP are excreted mostly as glucuronidated and sulfated conjugates (Krattenmacher, 2000). Two inactive metabolites of DRSP, 4,5-dihydro-DRSP-3-sulfate and an acid form of DRSP (Fig. 3), have also been identified in human plasma (Bachmann & Kopacz, 2009; Krattenmacher, 2000; Wiesinger, et al., 2015). While DRSP is also metabolized to four other metabolites by fungal cells (Table 1) (Quintana, et al., 2013), their biological activities and occurrence in humans remain unknown.

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4.2.9 DNG—Little is known about the metabolism of DNG. While it is predominantly found in serum in its unchanged form following oral administration (Wellington & Perry, 2002), DNG may be metabolized by CYP3A4 to various inactive metabolites which are rapidly eliminated from serum and excreted in urine (McCormack, 2010). Although the majority of these metabolites are unknown, at least one has been identified as 6β-hydroxy-DNG (Shin, et al., 2013) (Table 1), the biological function of which is unknown.

4.2.10 CPA—CPA is metabolized to 15β-hydroxy-CPA (Bhargava, et al., 1977) in humans, dogs and rhesus monkeys, and to 3α-hydroxy-CPA in rats (Kerdar, et al., 1995) (Table 1). Although the biological activity of 3α-hydroxy-CPA is unknown, 15β-hydroxy-CPA elicits similar anti-androgenic activity to CPA, but significantly weaker progestogenic activity (Kuhl, 2011).

4.3. Bioavailability

The terms availability and bioavailability are often confused. The former refers to how much of the drug is accessible to the cells (discussed later), while the latter refers to how much of the administered drug reaches the bloodstream after metabolism (Edelman, et al., 2010; Stanczyk, et al., 2013). Limited available data show that for all progestins except NES, most of the administered dose is available in circulation following metabolism (Table 2). The very low bioavailability of oral NES is presumably the reason why it is administered parenterally (Fraser, et al., 2005; Fraser, et al., 2007; Sitruk-Ware, 2006). Whether the bioavailability of NES or any of the other progestins is influenced by the route of delivery remains unknown.

4.4. Half-life

The contraceptive efficacy of a progestin is not only influenced by its bioavailability, but also by the time the progestin is present in the body to elicit a biological effect. This is reflected by half-life of a progestin, which refers to the time it takes for the maximum serum concentration to decrease to 50% (Stanczyk, et al., 2013). Progestins used in contraceptives exhibit a range of half-life values (Table 2). For example, the oral intake of NET results in a shorter half-life (2.5 – 12 hours) than NET administered intramuscularly (~278 hours) (Table 2). Similarly, a shorter half-life (24 hours) occurs for oral versus IM injection (~1200 hours) for MPA (Table 2). Interestingly, the half-lives for IM and SC administration of MPA in combination with E_2 did not significantly differ (~577 vs 742 hours) (Sierra-Ramirez, et al., 2011).

Although variable half-life values have also been reported for LNG, these do not appear to be significantly affected by dose or route of administration, or the presence of EE (Table 2). However, the half-life is much longer in obese than normal weight women using COCs containing LNG and EE (52.1 vs 25.6 hours; 73.6 vs 37.6 hours) (Edelman, et al., 2009; Westhoff, Torgal, Mayeda, Stanczyk, et al., 2010). Whether factors such as body weight also affect the half-life of other progestins is largely unknown. However, body weight does not appear to influence the half-life of MPA following administration of DMPA-SC (Jain, et al., 2004).

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The serum concentration of ETG is often measured in women using an oral contraceptive containing DSG and appears to not be influenced by route of administration, unlike limited data for NES (Table 2). Half-life values of GES are not influenced by dose (Table 2). Similar half-life values are obtained for DRSP and DNG, respectively, whether they are used alone or in combination with an estrogen (Table 2). Due to a paucity of data, similar conclusions could not be drawn for NGM and CPA (Table 2).

Taken together, the current data suggest that half-life is progestin-specific, and only sometimes dependent on dose, route of administration, whether estrogens are co-administered, and body weight. However, very limited data is available for most progestin formulations, and several have not been investigated for effects of all these variables. Finally, failure to detect differences in half-lives may be due to high inter-individual variability and resulting insufficient power of the studies.

4.5. Serum binding proteins

Availability of a specific concentration of progestin to the cells is dependent on its interaction with serum binding proteins such as corticosteroid binding globulin (CBG) and sex hormone binding globulin (SHBG). CBG preferentially binds and transports cortisol in the blood, while SHBG is a carrier protein for testosterone and/or estrogen (Pugeat, et al., 1981; Siiteri, et al., 1982). Steroid hormones bound to CBG and SHBG are unavailable to target tissues, while the unbound (free) steroids are available to elicit their biological effects in cells of target tissues.

Binding of progestins to CBG or SHBG not only influences the concentration of progestin available to target tissues, but may also result in the displacement of endogenous steroids from these proteins, thus increasing the availability of endogenous hormones free to elicit a biological response in target tissues. For example, NET, LNG, GES and ETG, unlike MPA, NGM, NES, DRSP, DNG and CPA, bind to SHBG to varying degrees (Table 3), suggesting that these progestins may compete with testosterone and/or estrogen for binding to SHBG and that only a fraction of bioavailable NET, LNG, GES and ETG will be available to target tissues. None of the progestins discussed in this review bind to CBG (Table 3), suggesting that progestins may not modulate the amount of cortisol available to target tissues via this mechanism.

Cortisol levels could however be influenced by progestins modulating the levels of CBG. Indeed, clinical studies indicate that oral contraceptive doses of NET (van der Vange, et al., 1990), LNG (Wiegratz, et al., 2003), DSG (Jung-Hoffmann, et al., 1992; Kuhl, et al., 1995), GES (Wiegratz, et al., 1995) and NGM (Wiegratz, et al., 1995) used in combination with EE, increase the serum concentration of CBG in healthy users. In contrast, 1 μM MPA, in the absence and presence of E_2, decreased CBG mRNA expression in a human endometrial cancer cell line (Misao, et al., 1998b).

MPA can also increase or decrease SHBG levels in a concentration-dependent manner in an endometrial cancer cell line. For example, low concentrations of MPA (0.1 nM) in combination with 10 nM E_2 increase the mRNA expression of SHBG, while higher concentrations of MPA (1 – 10 μM), in the absence or presence of 10 nM E_2, decrease

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SHBG mRNA expression (Misao, et al., 1998a). Furthermore, use of the injectable contraceptives DMPA-IM (Jeppsson, et al., 1982) and NET-EN (Zhao, et al., 1992) is associated with decreased SHBG levels in women. Interestingly, in women using COCs containing LNG and EE, the EE component increases SHBG levels, which leads to increased binding of LNG to SHBG, and decreased free LNG (Kuhnz, al-Yacoub, & Fuhrmeister, 1992; Kuhnz, Blode, et al., 1994). Combinations of EE with other progestins also elevate SHBG levels in women, for instance, in a vaginal ring containing ETG and EE (Fleischer, et al., 2009) as well as in COCs containing EE and DSG (Jung-Hoffmann, et al., 1992), GES (Wiegratz, et al., 1995), NGM (Wiegratz, et al., 1995), DNG (Oettel, et al., 1997), or DRSP (Batukan & Muderris, 2006). SHBG levels also increase in COCs containing DNG and E_2V (Di Carlo, et al., 1983). To the best of our knowledge, no information is available on binding of progestin metabolites to CBG and SHBG, or whether these metabolites can regulate the expression of these binding proteins.

Clearly there is a paucity of research on the influence of progestins used in contraception on SHBG and CBG levels. More research is needed to understand how the modulation of SHBG and/or CBG levels influence the freely available endogenous steroid hormone levels, as well as the concentrations of progestins freely available to elicit their biological effects in target cells or tissues. Moreover, as the majority of the above-mentioned studies focus on COCs rather than progestin-only contraceptives, further studies are needed to establish the relative roles of EE and/or specific progestins on regulation of serum binding protein levels.

5. Progestin concentrations in serum

Maintaining a concentration of progestin sufficient for contraceptive efficacy is essential for the duration of treatment. However, depending on the progestin, dose, method and route of administration, concentrations much higher than those required to maintain contraceptive efficacy are frequently attained and remain for variable lengths of time for some contraceptives. Concerns have arisen as to possible side-effects of such high concentrations (Hapgood, et al., 2018). To inform on these issues, maximal concentrations (C_{max}) are frequently reported, as well as the time taken to reach C_{max} (t_{max}), and concentrations at varying time intervals after first administration (Table 4). Long-acting injectable contraceptives typically exhibit a sharp peak in serum progestin levels a few days after injection, with concentrations much higher than required for contraceptive efficacy, which decrease with variable kinetics, and then remain fairly constant at levels just above contraceptive efficacy for a few months (Fig. 4) (Kirton & Cornette, 1974; Polis, et al., 2018). As the progestin serum half-life is shorter for COCs (Tamassia, et al., 1982), t_{max} is shorter for oral than injectable contraceptives. Hence daily administration is required to maintain levels above contraceptive efficacy. Long-acting progestins used in implants generally exhibit C_{max} values a few weeks after implantation due to slow release, but maintain levels of contraceptive efficacy for months or years (Sivin, et al., 2001; Wenzl, et al., 1998). Intravaginally administered contraceptives generally exhibit C_{max} values within hours of administration which decline and remain fairly constant over months or years, above levels required for contraceptive efficacy (Dogterom, et al., 2005; Timmer & Mulders, 2000). Table 4 summarizes some of these key pharmacokinetic parameters of progestins used in different HCs. A key issue, especially for contraceptives administered intravaginally,

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is the progestin concentrations in local tissue such as the FGT, where tissue-specific side-effects may occur. There is, however, little data on progestin levels within target tissues. A variety of methods have been used to measure progestin serum concentrations, including radioimmunoassay (RIA) and various liquid chromatography (LC) methods such as high performance liquid chromatography (HPLC) (Milano, et al., 1982; Read, et al., 1985), ultra-performance liquid chromatography (UPLC) (Thomas, et al., 2013; Westhoff, et al., 2012), either alone or coupled to a mass spectrometry instrument with one (LC-MS) or two mass analysers (LC-MS/MS). Gas chromatography (GC) or GC coupled to mass spectrometry (GC-MS) have also been used (Dikkeschei, et al., 1985; Jarvinen, et al., 1989; Kaiser, et al., 1974; Rossi, et al., 1979). Mass spectrometry methods are emerging as the method of choice for clinical samples as they offer the advantage of high sensitivity and specificity while being able to multiplex and measure levels of several progestins simultaneously (Abujrais, et al., 2019; Blue, et al., 2018; Buckner, et al., 2019; Cirrincione, et al., 2018; Laszlo, et al., 2019; Soldin & Soldin, 2009; Stanczyk & Clarke, 2010).

Although the pharmacokinetic parameters between different HCs (Table 4) depend on route of administration, progestin and dose, it is unclear to what extent differences are also affected by non-parallel investigations and differences in study design, including number of participants, their demographic characteristics (lactation, ethnicity, race, body mass index (BMI), weight and metabolism), duration on HC, and time and frequency of measurements. More strikingly, large inter-individual and inter-study variation in progestin C_{max} levels is generally reported for the same HC method. Whether these are due to some of the above-mentioned factors and/or different methods of quantification and/or steps prior to quantification is unclear from the literature. These large inter-study variations highlight the need for standardized methodologies, including specifications on solvents used for extraction of different progestins, methods of analysis and reporting of data (Stanczyk & Clarke, 2010; Stanczyk, et al., 2007).

Extensive tables showing data and sources from a comprehensive PubMed search of the literature on serum concentrations of progestins commonly used in contraception is available at Mendeley Data (http://dx.doi.org/10.17632/5sck77c9b9.1) [dataset]. Table 4 summarized these, while key points are discussed below.

5.1 Variations in serum progestin concentrations

5.1.1. MPA—C_{max} and t_{max} values for MPA in DMPA-IM users have been reported for only a few studies where sampling was conducted at frequent intervals p.i. (Kirton & Cornette, 1974; Ortiz, et al., 1977; U.S. Food and Drug Administration, 2003). These suggest that t_{max} is 3-6 days p.i. Studies not sampling in this interval may have underreported C_{max} values and incorrectly assigned t_{max}. A wide inter-study range of C_{max} values from 2.6-30 nM up to 65-100 nM is reported for 150 mg DMPA-IM (Table 4) [dataset]. More consistent values are reported for a plateau concentration of about 2.6 nM, which is maintained for 3 months (Mishell, 1996; Ortiz, et al., 1977). Besides large inter-study variability, large inter-individual variation occurs for MPA serum levels with DMPA-IM use, especially immediately after injection, as well as the shape of the pharmacokinetic profile. This is shown graphically for 3 women over 260 days following injection (Kirton &

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Cornette, 1974). Several studies reporting similar C_{max} values suggest that variation cannot be explained by different quantification methods (i.e. RIA versus LC-MS or GC-MS) (Bonny, et al., 2014; Fotherby, Saxena, et al., 1980; Shrimanker, et al., 1978).

For the three-monthly 104 mg MPA injection DMPA-SC, three studies measuring serum MPA levels over time report a t_{max} between 8-21 days after injection with a C_{max} range of 0.52-6.73 nM (Table 4) [dataset]. However, as for DMPA-IM, frequency of sampling times may not accurately reflect t_{max} or C_{max} if they occur within 0-8 days. Whether DMPA-SC is likely to have fewer side-effects than DMPA-IM due to the lower dose is unclear. Only two studies directly compare the two MPA formulations. One study assessed the levels of other reproductive hormones (E_2, P_4, follicle stimulating hormone) in parallel but not MPA levels (Jain, et al., 2004); the other study only directly compared MPA levels at 6 months, 1 year and 2 years (Kaunitz, et al., 2009), making it impossible to reliably compare their t_{max} and C_{max} values. To date, only one study has attempted measurement of MPA levels in cervical secretions. This study in DMPA-SC users had limited success, with only 4/8 samples giving detectable values (Buckner, et al., 2019).

5.1.2 NET—For the 200 mg IM injection of NET-EN, reported t_{max} values are 3-10 days and C_{max} ranged from 2.44-86 nM, with an upper range at 117 nM in one study (Table 4) [dataset]. The C_{max} values differ up to 48-fold, which is similar to the 38-fold range (2.6-99.6 nM) in C_{max} for MPA (Fotherby, Saxena, et al., 1980; Koetsawang, 1977; Smit, et al., 2004), and are consistent with high inter-individual differences in NET levels. However, as for MPA, chosen sampling times (earliest at 3 days) may not accurately capture t_{max} and C_{max} values. Reported steady-state NET levels of 0.39-14.6 nM are more variable than the 2.6 nM for DMPA-IM, which may in part be due to different sampling times for NET (30-120 days) (Fotherby, et al., 1978a, 1978b; Goebelsmann, et al., 1979). Serum NET levels after oral doses of ethynodiol acetate, which is metabolized to NET, also show wide ranges of serum NET levels (Cooke, et al., 1985; Vose, et al., 1979; Walls, et al., 1977), reflecting large biological variation. Limited data on NET levels in reproductive tissues show that NET is detectable in cervix, endometrium, myometrium (Reed, et al., 1973) and cervical mucus (Fels, et al., 2013).

5.1.3. LNG—LNG is commonly administered in many different HCs (Table 4) [dataset]. LNG administered in the IUD Mirena (52 mg LNG) generates serum LNG levels of 275-2430 pM at shorter time points (1-3 months), but slightly lower levels of 58-1620 pM after long-term use (1-8 years). However, there is little information on t_{max} and C_{max} for sampling times less than 1 month. LNG administered in the subdermal implant Norplant (36 mg LNG) has a reported t_{max} at 24 hours after insertion and a C_{max} of 0.8-11.3 nM. Later sampling times show lower serum LNG levels ranging from 0.4-1.3 nM (1 month-6 years) (Table 4). In COCs, LNG is administered at variable doses (100, 150, 250 μg or 1.5 mg) in combination with variable doses of EE (30 or 50 μg), resulting in large variation in reported serum LNG levels. For the 150 μg LNG + 30 μg EE COC (Nordette, Seasonique, Levora, Oralcon), t_{max} is reached at 1-2 hours and C_{max} is between 4.2-30 nM (Table 4).

LNG is one of the few progestins with literature available on levels in FGT tissue [dataset]. High but variable LNG levels were reported for the endometrium (808 ± 511 ng/g) of 4

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women receiving an IUD releasing 30 μg/day for 36-49 days (Nilsson, et al., 1982). In the same study, the authors measured 3.5 ng/g LNG in the endometria of two women receiving an oral dose of 250 μg/day LNG for 7 days, i.e. about 100-400 times lower than the IUD. Within the myometrium, fallopian tubes and fat tissue, LNG levels were comparable (1-5 ng/g) for both routes of administration (Nilsson, et al., 1982). Serum LNG levels were lower in the IUD group (647 ± 326 pM) compared to the oral group (1790 ± 669 pM). The differences in endometrial and serum LNG levels between the two groups may reflect differences in daily doses, routes for LNG to enter the blood for the different routes of administration, and likely accumulation of LNG in the endometrium. These results are consistent with a recent study showing higher LNG levels in cervical fluid compared to serum in Mirena users (Buckner, et al., 2019). However, more research on tissue LNG levels is required to make clearer conclusions.

5.1.4. ETG—ETG C_{max} levels for the implant Implanon rise from 820 ± 249 pM at 8 hours to 0.6-3.7 nM at 6 days, and a level of 2.76 nM in the first few weeks (Table 4) [dataset]. After long-term use of 3 months-3 years, serum ETG levels range from 481-2470 pM. In a study comparing Implanon (ETG) and Norplant (LNG), serum LNG showed greater individual variation (0.3-6 nM) compared to serum ETG (0.9-3.7 nM), especially within the first 7 days after insertion (Makarainen, et al., 1998). Serum ETG levels after oral administration of 150 μg DSG together with 30 μg EE, range from 4.62-19.1 nM depending on time of sampling (1.5 hours-21 days) (Table 4) [dataset]. Likewise, ETG serum levels following insertion of the NuvaRing IVR are also dependent on time of sampling (2 days-5 weeks) and range from 2.1-7.76 nM (Table 4) [dataset].

5.1.5. NES—Serum NES levels after IVR insertion range from 99-134 pM (15 days-6 months) for the 50 μg IVR, and 250-350 pM (21 days-25 weeks) for the 150 μg IVR, also containing 15 μg EE (Table 4) [dataset]. For implants containing around 80 mg NES, serum levels range from 60-259 pM depending on time of sampling (1-12 months) (Table 4) [dataset].

5.1.6. Other progestins—Very little information is available for serum levels of the less-commonly used progestins (Table 4) [dataset]. While there are more studies for some progestins (GES, DRSP, DNG) than others (NoMAc, megestrol acetate (MA), NGMN, CPA), collectively the available studies indicate that a wide range of variation in serum levels also occurs for these less well-studied progestins. For instance, levels of NoMAc administered in the COC containing 2.5 mg NoMAc plus 1.5 mg E_2 reach a C_{max} of 19.5-33.2 nM (Table 4), while a C_{max} range of 6.8-48.3 nM is reached following administration of COC containing 75 μg GES plus 30 μg EE (Table 4). DRSP, typically administered in a COC containing 3 mg DRSP plus 20-30 μg EE (Yaz, Yasmin), generates serum levels of 2-298 nM DRSP, although this variation appears to depend on time of sampling (Table 4). DNG administered in a COC containing 2 mg (with or without 2 mg E_2V or 30 μg EE) generated serum DNG levels ranging from 73.9-206 nM (Table 4). For most COCs, t_{max} is reached within the first 3 hours post administration (Table 4). Together, the abovementioned data again highlight the variability of serum progestin levels between studies, different routes of administration and timing of sample measurements.

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5.2. Effects of duration on contraceptives on serum progestin levels

The length of time on HC may be relevant to interpreting C_{max} serum progestin values, since these may be influenced by progestin accumulation, rate of clearance, bioavailability and metabolism. However, studies stratifying contraceptive users based on different durations on contraception and longitudinal studies are lacking. Oral MPA is reported to accumulate due to its slow elimination half-life of 2.5 days (Pollow, et al., 1989). More extensive literature on DMPA-IM is, however, contradictory. One study suggests that MPA levels after 12 weeks p.i do not vary with the number of injections over 4.4-10.6 years (Jeppsson, et al., 1982), similar to results from another study comparing the first and fifth injection cycles of DMPA-IM (Schwallie, 1974). However, another study showed a trend of slightly increased MPA levels after longer (4-5 years: 0.5-1.6 ng/ml) compared to shorter (1 year or less: 0.3-1.5 ng/ml) duration of use, although there was wide inter-individual variability (Smit, et al., 2004). Other studies on DMPA-IM also suggest slightly higher levels occur in serum after repeated injections (Koetsawang, et al., 1979; U.S. Food and Drug Administration, 2003). For the lower dose monthly injectable Cyclofem (25 mg MPA + 5 mg E_2C), serum MPA levels were higher in women who had received 31-45 injections (3.41 ± 0.19 nM) compared to those who had received only one (2.65 ± 0.13 nM) (Koetsawang, et al., 1979). A recent study, however, showed steady state MPA levels of 1.11 nM after two months (Thurman, et al., 2013). In agreement with another study (Zhou, et al., 1998), no accumulation was observed once steady state was attained. For example, women receiving multiple doses of NET-EN (5-11 injections) required a longer mean time for serum NET levels to fall below detection or 0.2 nM (152 days) than women who received only a single dose (107 days) (Fotherby, et al., 1978b). In this study, mean NET levels were higher at 90 days (2.44 nM) in multiple-injection users compared to levels at 70 days (1.22 nM) in single-dose users (Fotherby, et al., 1978b). Together these results suggest that progestin serum levels may change with duration of contraceptive use for the injectables DMPA-IM and NET-EN. However, limited data on cumulative effects exists for most HCs, while for the available data it is unclear to what extent detected differences are due to unmatched populations, given the high inter-individual variability in serum concentrations.

5.3 Effects of demographic/intrinsic factors on serum progestin levels

Studies on progestin serum levels usually record the BMI of the women in their cohort. Recent reviews on the efficacy of contraceptives in obese women (Simmons & Edelman, 2016; Stanczyk, et al., 2018) conclude that, in general, contraceptive efficacy is not affected in obese women. It does not, however, follow that progestin concentrations are not affected by BMI, since many HCs use progestin doses above the threshold needed for contraceptive efficacy (Cherala, et al., 2016). Use of BMI as an index has limitations including its inability to distinguish between muscle and fat mass and “body type”. For example, Asian women are generally smaller in height and lower in body weight compared to European women and could have similar BMIs but smaller “body type”. Comparisons based on ethnicity thus may also be comparing differences in “body type” for similar BMIs. Comparisons between ethnic groups may also be influenced by population pharmacogenetics and pharmacogenomics, such as variations in allelic frequencies of drug metabolism enzymes (Kobayashi, et al., 2000). Consistent with this, large variations in drug metabolizing enzyme allelic frequencies have been reported in African populations (Dandara, et al., 2011; Ikediobi, et al., 2011),

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Results of studies investigating the relationship between progestin serum levels in women and their BMI vary for different HCs. Several studies have found a link between higher BMI and/or weight and lower progestin concentrations for women on HCs such as the ETG implant (Implanon), LNG rod (Norplant) and LNG IUD (Mirena) (Huber & Wenzl, 1998; Mornar, et al., 2012). However, studies on ETG implants in American women of different ethnicities (McNicholas, et al., 2015) and in a population of primarily Hispanic women (Morrell, et al., 2016) did not detect such a link. For women on NET-EN, DMPA-IM or DMPA-SC, most studies also find no link between BMI and progestin concentration (Fotherby & Koetsawang, 1982; Jain, et al., 2004; Lan, et al., 1984; Nanda, et al., 2016; Smit, et al., 2004). Limited data do, however, suggest a possible link between ethnicity and/or "body type" and progestin concentrations. Higher initial NET but not MPA serum levels were observed in Indian women compared to Swedish women, although sample sizes were small, and body weight, but not height or BMI, were reported (Fotherby, Saxena, et al., 1980). Since Indian women have BMIs 1-2.5 kg/m^2 lower than the global average (Finucane, et al., 2011), higher serum NET levels may correlate with lower BMI. Many of the studies reporting the upper range of DMPA-IM C_{max} values were carried out in Thai women (Fotherby & Koetsawang, 1982; Koetsawang, 1977; Shrimanker, et al., 1978), suggesting that women of smaller “body type” may be exposed to higher levels of progestin, with possible higher side-effect risks. However, to our knowledge there are no studies comparing C_{max} for DMPA-IM in Thai and non-Thai women. Together, most studies do not show a link between BMI and progestin levels. However, there are some inconsistencies in the literature and more data is thus required. Apart from the abovementioned studies observing serum levels in relation to weight or population for select progestins, most studies have failed to address the effect of “body type” on serum progestin levels. The question whether lactation has an effect on serum progestin levels has also arisen. For MPA, two studies using RIA report lactating women receiving DMPA-IM show very high serum MPA levels of 78 nM in Chinese women (range 42-78 nM) (Fang, et al., 2004) and up to 99.6 nM in Thai women (range 24.3-99.6 nM) (Koetsawang, 1977) after the first week p.i. Interestingly, another study in non-lactating Thai women reported lower serum MPA levels of 4.4-23.3 nM one week after injection, also using RIA (Shrimanker, et al., 1978). However, to date, no direct comparison between lactating and non-lactating women of the same ethnicity receiving MPA or other progestin contraceptives has been made within the same study, using the same method of quantification. It is therefore unclear whether lactating women have different progestin serum levels than non-lactating women.

6. Conclusions and Research Gaps

Understanding metabolism and pharmacokinetics of progestogens in women is important for understanding dose requirements for contraceptive efficacy, and the potentially beneficial or detrimental effects of progestogens and/or their metabolites in women. Evidence is emerging that metabolism is influenced by the route of administration i.e. orally or parenterally, that different steroid-metabolising enzymes are expressed in peripheral tissues, that some progestins generate more metabolites than others, and that several progestin metabolites have biological activities via the PR and/or other members of the SR family. Interestingly, some progestins also generate estrogenic metabolites that may provide additional beneficial

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or detrimental effects. It is clear from the relatively little information available that more research is required on the identification of cell- and tissue-specific progestin metabolites, metabolizing enzymes and the biological activities of metabolites. This may be particularly relevant for susceptibility to STIs for progestins administered in the genital tract as well as for reproductive tissue cancers for all progestins and methods of administration. Most progestins have similar bioavailabilities when delivered orally but the effect of route of administration remains underexplored. Substantial data are available on progestin half-lives, which appear to sometimes depend on type and dose of progestin, route of administration, whether it is co-administered with an estrogen and body weight. Whether differences in half-life are masked by inter-individual differences are however underexplored. While some information is available on differential effects of COCs on the regulation of CBG and SHBG levels as well as endogenous steroid levels via binding to these proteins, data are scant for progestins, especially as used in progestin-only contraceptives, and no information is available for progestin metabolites. Substantial information is available about serum concentrations of some but not other progestins used in different forms of contraception. Several HCs result in serum progestin concentrations above those required for contraceptive efficacy and development of HCs using lower doses for minimal side-effects requires further investigation. Determination of real differences in serum concentrations between methods is hampered by high inter-individual variability within studies for some methods, different sampling times and methods of detection, different demographic characteristics of study populations, varying number of participants in the studies being compared, and a tendency to compare results of non-parallel studies. What is clear, however, is that high inter-individual variability in serum concentrations for some methods of contraception suggest that side-effects may be different for different women using the same method, given that SR responses are highly dose-dependent. Moreover, very little information is available about progestins or their metabolite concentrations in tissue or FGT fluids, which requires more investigation, since the relative levels may be very different and progestin-dependent. While there is evidence that duration of contraceptive use affects serum levels for some methods, the effects of intrinsic participant factors on serum levels are unclear from the literature. BMI does not appear to detectably influence MPA serum levels in injectable DMPA users, while the effect for other methods is less clear. Research gaps include addressing the effects of intrinsic factors such as body size, height and lactation on serum progestin levels. This may be particularly important for injectable contraceptives such as DMPA-IM, where side-effects may depend critically on initial peak serum concentrations which may be determined by such intrinsic factors. The identification of important questions to be investigated will depend on the particular contraceptive method and its known clinical risk profile. Basic mechanistic research to establish proof of concepts and hypotheses for testing on clinical samples would be invaluable in this regard. Minimizing confounding intrinsic factors of study participants and standardization of methodologies for sample collection and detection by high throughput methods should enable many of the above research gaps to be filled.

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Abbreviations

BMI	body mass index
CBG	corticosteroid binding globulin
COC	combined oral contraceptive
CPA	cyproterone acetate
DNG	dienogest
DRSP	drospirenone
DSG	desogestrel
E_2	estradiol
E_2C	estradiol cypionate
E_2V	estradiol valerate
EE	ethinyl estradiol
ETG	etonogestrel
GES	gestodene
HC	hormonal contraception
IM	intramuscular
IVR	intravaginal ring
LNG	levonorgestrel
MA	megestrol acetate
MPA	medroxyprogesterone acetate
MS	mass spectrometry
NGM	norgestimate
NGMN	norelgestromin
NES	nestorone
NET	norethisterone/norethindrone
NET-A	NET acetate
NET-EN	NET enanthate

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NoMAc	nomegestrol acetate
P_4	progesterone
p.i.	post-injection
RIA	radioimmunoassay
SC	subcutaneous
SHBG	serum hormone binding globulin
SR	steroid receptor

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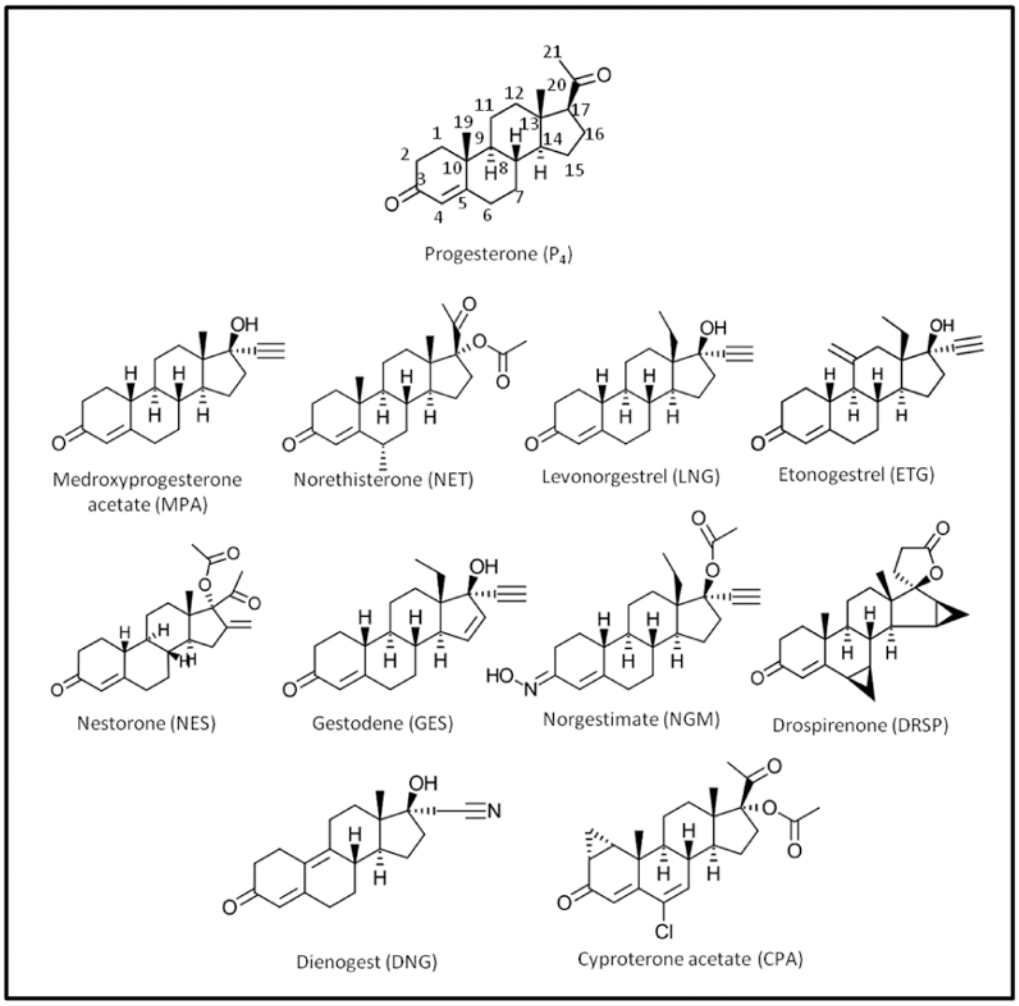

Figure 1. Chemical structures of P_4 and progestins commonly used in contraception.
For P_4, the letters 1-21 denote the carbon number.

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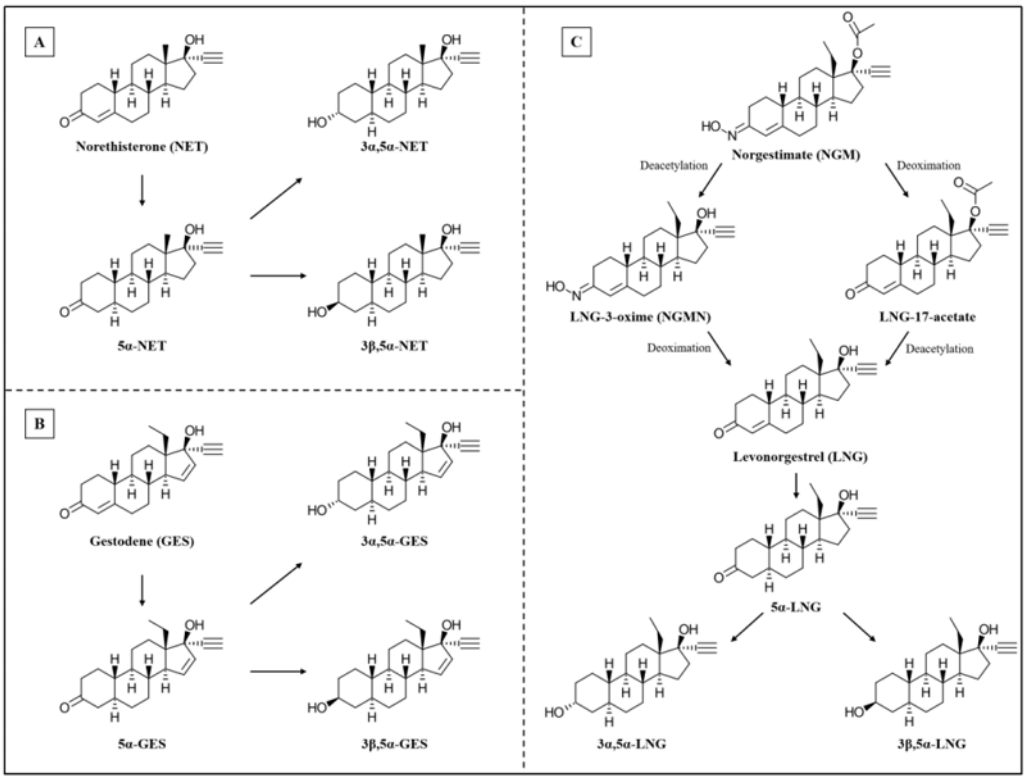

Figure 2. Structures of (A) NET, (B) GES, (C) NGM and LNG, and their respective metabolites
(A and B are redrawn from (Larrea, et al., 2001); C is adapted from (Garcia-Becerra, et al., 2002; Juchem, et al., 1993)).

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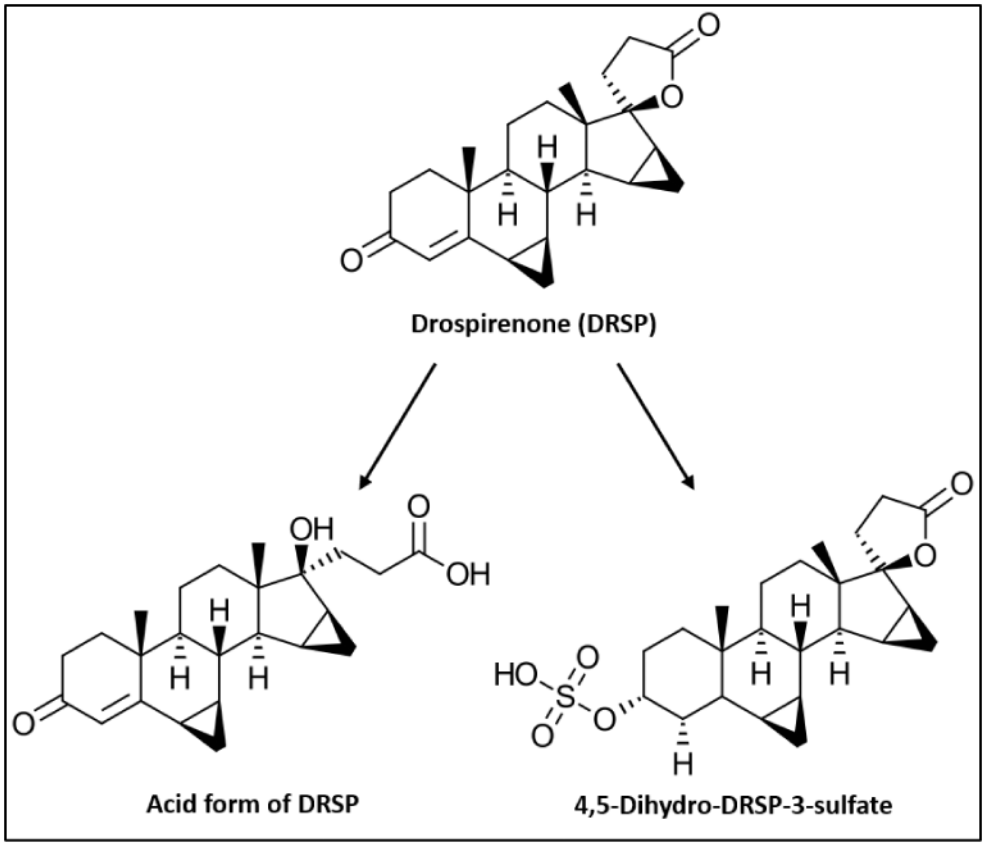

Figure 3. Structure of DRSP and its metabolites, an acid form of DRSP and 4,5-dihydro-DRSP-3-sulfate

(redrawn from (Krattenmacher, 2000)).

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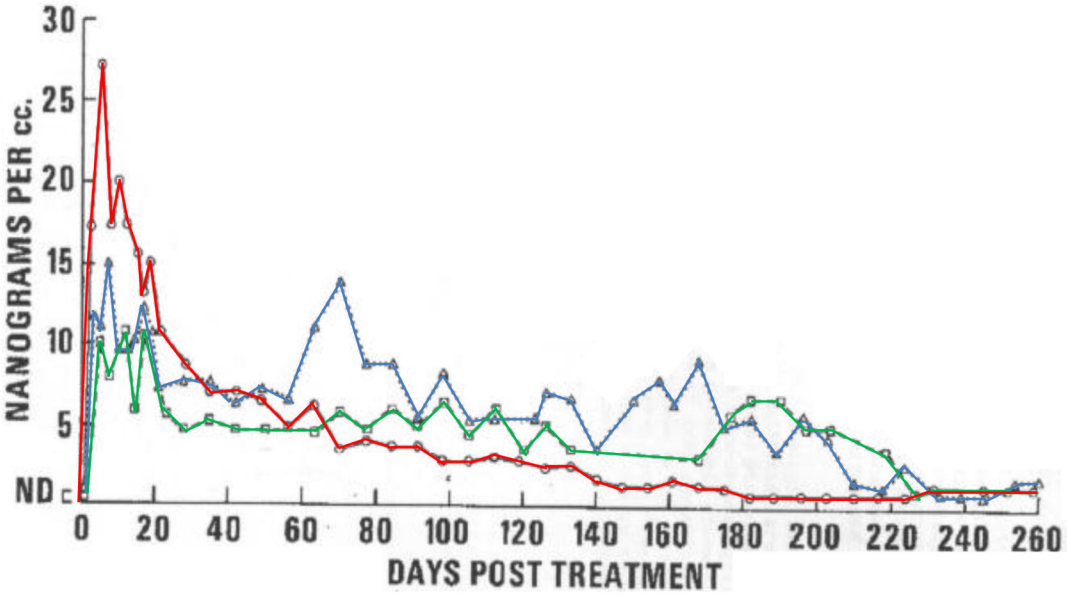

Figure 4. Large inter-individual variability occurs for C_{max}, steady-state values and shape of the pharmacokinetic profile in DMPA-IM users.

Serum MPA levels in 3 women (red, green and blue lines) over 260 days following a single injection of DMPA-IM, as measured by direct RIA (adapted with permission from (Kirton & Cornette, 1974)).

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TABLE 1.

Metabolites of progestins commonly used in contraception

Progestin	Metabolites	Active compound	Reference(s)
MPA	1β-hydroxy-MPA[$]; 2β-hydroxy-MPA[$]; 6β-hydroxy-MPA[$]; 6β, 21-dihydroxy-MPA[$]	MPA	(Fukushima, et al., 1979; Helmreich & Huseby, 1962; Sturm, et al., 1991; Zhang, et al., 2008)
NET-EN	NET; EE	NET; EE	(Bayer Healthcare Pharmaceuticals Inc, 2011; Stanczyk & Roy, 1990)
NET	5α-NET; 5β-NET; 3α,5α-NET; 3β,5α-NET; 3α,5β-NET; 3β,5β-NET; EE	5α-NET; 3α,5α-NET; 3β,5α-NET; NET; EE	(Blom, et al., 2001; Chu, et al., 2007; Chwalisz, et al., 2012; Garcia-Becerra, et al., 2004; Kuhl, 2005; Kuhl & Wiegratz, 2007; Kuhnz, et al., 1997; Larrea, et al., 2001; Lemus, et al., 2009; Reed, et al., 1990; Schoonen, et al., 2000; Stanczyk, 2003; Stanczyk & Roy, 1990)
LNG	5α-LNG; 5β-LNG; 3α,5α-LNG; 3β,5α-LNG; 3α,5β-LNG; 3β,5β-LNG; 2α-hydroxy-LNG; 16β-hydroxy-LNG; 16β-hydroxy-3α,5β-tetrahydro-LNG	5α-LNG; 3α,5α-LNG; 3β,5α-LNG; LNG	(Garcia-Becerra, et al., 2002; Garcia-Becerra, et al., 2004; Larrea, et al., 2001; Schoonen, et al., 2000; Stanczyk, 2003; Stanczyk & Roy, 1990)
GES	5α-GES; 3α,5α-GES; 3β,5α-GES; 1β-hydroxy-GES; 6α-hydroxy-GES; 11α-hydroxy-GES; 11β-hydroxy-GES	5α-GES; 3α,5α-GES; 3β,5α-GES; GES	(Garcia-Becerra, et al., 2004; Larrea, et al., 2001; Lemus, et al., 2001; Stanczyk & Roy, 1990; Ward & Back, 1993)
NGM	Norelgestromin; Norgestrel (LNG)	Norelgestromin; LNG	(Juchem, et al., 1993; Madden, et al., 1990; McGuire, et al., 1990; Phillips, et al., 1990; Prifti, et al., 2004; Stanczyk, 2003)
ETG	6β-hydroxy-11,22-epoxy-ETG[*]; 11,22-epoxy-ETG[*]; 10β-hydroxy-ETG[*]; 6β-hydroxy-ETG[*]; 14α-hydroxy-ETG[*]	ETG	(Baydoun, et al., 2016)
NES	17α-deacetyl-NES[#]; 4,5-dihydro-17α-deacetyl-NES[#]	NES	(Kumar, et al., 2017; Prasad, et al., 2010)
DRSP	4,5-dihydro-DRSP-3-sulfate; acid form of DRSP; 6β,7β,15β,16β-dimethylene-11α-hydroxy-3-oxo-l7α-pregn-4-en-21,17-carbolactone[**]; 6β,7β,15β,16β-dimethylene-11α-hydroxy-3-oxo-l7β-pregn-4-en-21,17-carbolactone[**]; 6β,7β,15β,16β-dimethylene-11β-hydroxy-3-oxo-l7α-pregn-4-en-21,17-carbolactone[**]; 6β,7β,15β,16β-dimethylene-2β-hydroxy-3-oxo-l7α-pregn-4-en-21,17-carbolactone[**]	DRSP	(Bachmann & Kopacz, 2009; Krattenmacher, 2000; Quintana, et al., 2013; Wiesinger, et al., 2015)
DNG	6β-hydroxy-DNG[$]	DNG	(Shin, et al., 2013)
CPA	15β-hydroxy-CPA; 3α-hydroxy-CPA	15β-hydroxy-CPA; CPA	(Bhargava, et al., 1977; Kerdar, et al., 1995; Schindler, et al., 2003)

[$] Activity of metabolites unknown.

[*] ETG hydroxylation in fungi (*Cunninghamella blakesleeana* and *C. echinulate*). Presence and physiological relevance in humans not known.

[#] NES metabolism in rats administered by subcutaneous injection. Presence and physiological relevance in humans not known.

[**] DRSP is metabolised in fungal cells (*Absidia corymbifera, BAFC 1072, A. coerulea* and *Syncephalastrum racemosum*). Presence and physiological relevance in humans not known.

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TABLE 2.

Reported bioavailabilities and half-lives of progestins commonly used in contraception

Progestin	Route of administration	Dose (mg)	Bioavailability (%)	Half-life (h)	Reference(s)
MPA	Oral	10	100	24	(Schindler, et al., 2003; Stanczyk, et al., 2013; Victor & Johansson, 1976)
	Intramuscular Injection	150	ND	~1200	(Pfizer, 2016b)
		25 (+ 5 E_2C)	ND	~577	(Sierra-Ramirez, et al., 2011)
	Subcutaneous Injection	104	ND	~854.4 - 1125.6	(Jain, et al., 2004; Pfizer, 2016a; Segall-Gutierrez, et al., 2010)
		25 (+ 5 E_2C)	ND	~742	(Sierra-Ramirez, et al., 2011)
		50	ND	~753.6	(U.S. Food and Drug Administration, 2003)
		75		~763.2	
		100		~648	
		150		~895.2	
NET-EN	Intramuscular Injection	200	50.2	278.4	(Sang, et al., 1981)
NET	Oral	0.350	64	5 - 12	(Pfizer, 2005; Prasad, et al., 1979)
		0.7	ND	2.5	(Kuhl, et al., 1982)
		1	64	8	(Back, et al., 1978)
		1 (+ 0.05 EE)	64	7.6	(Back, et al., 1978; Shi, et al., 1987)
LNG	Oral	0.75	ND	20.2-24.4	(Kook, et al., 2002; Sambol, et al., 2006; Tremblay, et al., 2001)
		0.100 (+ 0.020 EE)	ND	25.6 – 70.7[@]	(Edelman, et al., 2009; Edelman, et al., 2014)
		0.150 (+ 0.030 EE)	89	18.4 - 73.6	(Back, et al., 1981; Edelman, et al., 2014; Frey, et al., 2016; Humpel, et al., 1978; Kuhnz, al-Yacoub, & Fuhrmeister, 1992; Westhoff, Torgal, Mayeda, Pike, et al., 2010)
		0.250 (+ 0.050 EE)	100	11.9[$*$] – 20.6[*#*]	(Back, et al., 1981; Back, Grimmer, Rogers, et al., 1987; Kuhnz, Blode, et al., 1994)
		Day 1-6: 0.050 (+ 0.030 EE) Day 7-11: 0.075 (+ 0.040 EE) Day 12-21: 0.125 (+ 0.030 EE)	ND	20.9 – 23.4	(Kuhnz, Staks, et al., 1994)
	Intravenous Injection	0.030	87	1.6	(Humpel, et al., 1978)
		0.250 (+ 0.050 EE)	88	13.8	(Back, Grimmer, Rogers, et al., 1987)

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Progestin	Route of administration	Dose (mg)	Bioavailability (%)	Half-life (h)	Reference(s)
	Intrauterine Device	52 *	ND	17 - 20	(Bayer Healthcare Pharmaceuticals Inc, 2013, 2014)
	Implant	75 **	ND	13 - 18	(Population Council, 2002)
		36	ND	13 - 18	(Sivin, et al., 1997; Wyeth Pharmaceuticals)
	Vaginal	0.250 (+ 0.050 EE) (tablet)	99	15.6	(Back, et al., 1981; Back, Grimmer, Rogers, et al., 1987)
		0.750 per 4ml (gel)	ND	34	(Sitruk-Ware, et al., 2007)
		1.5 per 4 ml (gel)	ND	29.9	(Sitruk-Ware, et al., 2007)
GES	Oral	0.075 (+ 0.030 EE)	87 - 99	12 – 15	(Bayer Healthcare Pharmaceuticals Inc, 2010a; Orme, et al., 1991; Stanczyk & Archer, 2014)
		Day 1-6: 0.050 (+ 0.030 EE) Day 7-11: 0.070 (+ 0.040 EE) Day 12-21: 0.10 (+ 0.030 EE)	100	16 – 21.9	(Bayer Healthcare Pharmaceuticals Inc, 1991; Kuhnz, Baumann, et al., 1993)
		0.06 (+ 0.015 EE)	ND	12 - 20	(Bayer Healthcare Pharmaceuticals Inc., 2000)
NGM (active NGMN metabolite administered)	Transdermal Patch	6 (+ 0.75 EE) *#	ND	26.1 – 30.1	(Abrams, et al., 2002; Ortho-McNeil-Janssen Pharmaceuticals Inc, 2010; Taneepanichskul, 2005)
ETG	Oral	0.150 (+ 0.030 EE)	76 – 79.2	11.9 – 30.6	(Back, Grimmer, Shenoy, et al., 1987; Bergink, et al., 1990; Orme, et al., 1991; Timmer & Mulders, 2000; Timmer, et al., 1999)
	Intravenous Injection	0.150	100	32.2	(Timmer, et al., 1999)
		0.150 (+ 0.030 EE)	62 - 100	12.6 - 28.4	(Huber & Wenzl, 1998; Stanczyk, 2003; Timmer & Mulders, 2000)
	Implant	68 #	100	25	(Merck and Co. Inc, 2017)
	Vaginal Ring	11.7 (+ 2.7 EE) ##	102.9	29.3	(Organon USA Inc, 2005; Timmer & Mulders, 2000)
NES	Oral	0.100	10 – 11.3	1	(Noe, et al., 1993)
	Intravenous Injection	0.100	ND	0.06 – 1.38	(Noe, et al., 1993)
	Transdermal Spray	3 x 90 µl	ND	26.8 – 41.6	(Fraser, et al., 2007)
DRSP	Oral	3 (+ 0.020 EE)	76	30	(Bachmann & Kopacz, 2009; Fenton, et al., 2007; Perez-Lopez, 2008)
		6	93.85	30.8 – 32.5	(Bhaumik, 2008)
DNG	Oral	2	91	9 - 11	(Bayer Healthcare Pharmaceuticals Inc, 2010b; McCormack, 2010; Shin, et al., 2013)
		2 (+ 0.030 EE)	90	7.5 - 9	(Foster & Wilde, 1998; Perez-Campos, 2010)
		2 tablets: 0 (+ 3 E_2V); 5 tablets: 3 (+ 2 E_2V); 17	91	10.8	(Borgelt & Martell, 2012; Wellington & Perry, 2002)

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Progestin	Route of administration	Dose (mg)	Bioavailability (%)	Half-life (h)	Reference(s)
		tablets: 3 (+ 2 E_2V); 2 tablets: 0 (+1 E_2V)			
CPA	Oral	2 (+ 0.050 EE)	100	40.8 – 78.6	(Humpel, et al., 1977; Kuhnz, Staks, et al., 1993; Schindler, et al., 2003)

ND – not determined. The information in the brackets indicates the type and concentration of the estrogen component used in the progestin-estrogen combined contraceptive.

*Initial release rate of 20 μg per day reduced to ~10 μg per day after 5 years.

**Initial release rate of two rods, each containing 75 mg, is ~100 μg per day. After 12 months it decreases to ~40 μg per day, and after 24 months to ~30 μg per day.

#Initial release rate of 60 -70 μg/day (week 5 – 6), decreases to ~35 -45 μg per day after 1 year, ~30 – 40 μg per day after 2 years and ~25 – 30 μg per day after 3 years.

##Release rate of ~0.120 mg ETG and ~0.015 mg EE per day for three weeks.

*#Release rate of ~0.150 mg NGMN and ~0.020 mg EE per 24 hours.

@Large standard deviation (SD) observed in $t_{1/2}$ values (70.7 ± 50.4 hours).

$Large SD observed in $t_{1/2}$ values (59.4 ± 26.6 hours).

$*$Serum concentration of LNG measured using GC-MS and pharmacokinetic parameters evaluated using software package TOPFIT (Thomae GmbH, Germany).

*#*Serum concentration of LNG measured using RIA and pharmacokinetic parameters evaluated using WinNonLin (v 5.2; Pharsight, Moutain View, CA).

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TABLE 3.

Percentage binding of progestins to steroid-binding proteins present in blood and percentage of the progestin available to target tissues

Progestin	SHBG-bound (%)	CBG-bound (%)	Albumin-bound (%)	Free (%)	Available (%)	Reference(s)
MPA	0	0	88	12	100	(Kuhl, 2011; Schindler, et al., 2003)
NET	35.5	0	60.8	3.7	64.5	(Hammond, et al., 1982; Kuhl, 2011)
LNG	47.5 64.1 - 68.3 [*] 55 - 73.6 [#]	0	50 30.5 - 34.6 25.5 - 43.6	2.5 1.1 - 1.3 0.9 - 1.4	52.5 31.6 - 35.9 26.4 - 45	(Fotherby, 1990; Hammond, et al., 1982; Kuhl, 2011; Kuhnz, al-Yacoub, & Fuhrmeister, 1992; Kuhnz, Blode, et al., 1994; Kuhnz, Staks, et al., 1994; Stanczyk, 2003)
GES	57 – 81.5	0	17.9 – 41.3	0.6 – 1.8	18.5 – 43.1	(Kuhnz, Baumann, et al., 1993; Kuhnz, Schutt, et al., 1992)
NGM/NGMN	0	0	97.2	2.8	100	(Hammond, et al., 2003; Kuhl, 2011)
ETG	15 32	0	63.5	4.5	68	(Fotherby, 1990; Kuhl, 2011; Kuhnz, et al., 1990)
NES	0	0	87	13	100	(Fotherby, 1990; Kuhl, 2011)
DRSP	0	0	95 - 97	3 - 5	100	(Kuhl, 2011; Schindler, et al., 2003)
DNG	0	0	90	10	100	(Foster & Wilde, 1998; Kuhl, 2011; McCormack, 2010)
CPA	0	0	93	7	100	(Kuhl, 2011; Schindler, et al., 2003)

[*] Increased binding of LNG to SHBG in women using Microgynon® 30 (150 μg LNG and 30 μg EE) for 3 months.

[#] Increased binding of LNG to SHBG in women using Triquilar® ED (day 1-6: 50 μg LNG and 30 μg EE; day 7-11: 75 μg LNG and 40 μg EE; day 12-21: 125 μg LNG and 30 μg EE) for 3 months.

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TABLE 4:

Systemic concentrations of progestins.

Progestin	Route of administration	Dose (mg)	C_{max}* (nM)	T_{max}	References
MPA	Oral	10	3.0-13.3	1-4 hours	(Hiroi, et al., 1975; Victor & Johansson, 1976)
	Intramuscular Injection	150	2.6-99.6	3-6 days	(Bassol, et al., 1984; Bonny, et al., 2014; Cohn, et al., 2007; Fang, et al., 2004; Fotherby, Koetsawang, et al., 1980; Fotherby, Saxena, et al., 1980; Jeppsson, et al., 1982; Kirton & Cornette, 1974; Koetsawang, 1977; Mishell, 1996; Nanda, et al., 2016; Ortiz, et al., 1977; Virutamasen, et al., 1996)
		25 (+ 5 E_2C)	0.9-6.5	3-3.5 days	(Aedo, et al., 1985; Rahimy, et al., 1999)
	Subcutaneous Injection	104	0.5-6.7	8 -21 days	(Halpern, et al., 2014; Jain, et al., 2004; Segall-Gutierrez, et al., 2010; Toh, et al., 2004; U.S. Food and Drug Administration, 2003)
NET-EN	Intramuscular Injection	200	2.4-117	3-10 days	(Fotherby, et al., 1978b; Fotherby & Koetsawang, 1982; Fotherby, Saxena, et al., 1980; Friedrich, et al., 2018; Goebelsmann, et al., 1979; Kuhl, 1990; Lahteenmaki, et al., 1983; Pyra, et al., 2018; Sang, et al., 1981)
NET	Oral	0.350	15.7-49.6	1-2 hours	(Prasad, et al., 1979)
		1	0.7-33.5	1-2 hours	(Kuhl, 1990; Warren & Fotherby, 1974)
		1 (+ 0.05 EE)	5.7-69.7	24 hours	(Shi, et al., 1987; Sivakumar, et al., 1989)
LNG	Oral	0.75	19.3-69.8	1.5-2.5 hours	(Kook, et al., 2002; Tremblay, et al., 2001)
		1.5	8.7-84.8	0-5 hours	(Praditpan, et al., 2017; Theron, et al., 2004)
		0.100 (+ 0.020 EE)	0.3-65.6	0.5-4 hours	(Depypere, et al., 2019; Edelman, et al., 2009)
		0.150 (+ 0.030 EE)	4.2-30	1-2 hours	(Back, et al., 1981; Basaraba, et al., 2017; Frey, et al., 2016; Kuhnz, al-Yacoub, & Fuhrmeister, 1992; Licea-Perez, et al., 2007; Westhoff, Torgal, Mayeda, Pike, et al., 2010)
		0.250 (+ 0.050 EE)	14.6-17.7	1.23 hours	(Abdalla, et al., 1992; Back, Grimmer, Rogers, et al., 1987)
	Intrauterine Device#	52	0.3-2.4	1-3 months	(Hidalgo, et al., 2009; Selim & Hussein, 2013)
	Implant#	75	1.3-2.1	1 month	(Croxatto, 2002; Sivin, et al., 2001)
		36	0.8-11.3	24 hours	(Croxatto, et al., 1985; Darney, et al., 1996; Munro, et al., 1996; Sivin, et al., 1997)
	Vaginal	0.250 (+ 0.050 EE) (tablet)	221	24 hours	(Abdalla, et al., 1992; Back, Grimmer, Rogers, et al., 1987)
		0.750 per 4ml (gel)	12.0-16.2	12 hours	(Sitruk-Ware, et al., 2007)
		1.5 per 4 ml (gel)	9-14.4	6 hours	(Sitruk-Ware, et al., 2007)
GES	Oral	0.075 (+ 0.030 EE)	6.8- 48.3	1-2 hours	(Bayer Healthcare Pharmaceuticals Inc, 2010a; Dibbelt, et al., 1992; Kuhl, et al., 1988a)

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Progestin	Route of administration	Dose (mg)	C_{max}* (nM)	T_{max}	References
NGM (active NGMN metabolite administered)	Transdermal Patch	0.150 (+ 0.030 EE)	1.8-5.3	72 hours	(Abrams, et al., 2002)
	Oral	0.250 (+ 0.035 EE)	6.5	48 hours	(Hammond, et al., 2003)
ETG	Implant#	68	0.6-3.7	6 days	(Bennink, 2000; McNicholas, et al., 2015; Mornar, et al., 2012; Morrell, et al., 2016; Wenzl, et al., 1998)
	Vaginal Ring	0.120 (+ 0.015 EE)	2.1-7.8	2 days-5 weeks	(Buckner, et al., 2019; Dogterom, et al., 2005; Timmer & Mulders, 2000)
	Oral	0.150 DSG (+ 0.030 EE)	4.62-19.1	1.5 hours-21 days	(Kuhl, et al., 1988b; Kuhnz, al-Yacoub, Power, et al., 1992; Kuhnz, Schutt, et al., 1992)
NES	Subcutaneous capsule	0.04	0.3-27.3	7-9 months	(Lahteenmaki, et al., 1981; Lahteenmaki, et al., 1982)
	Implant#	80	0.06-0.26	1-12 months	(Brache, et al., 2000; Laurikka-Routti & Haukkamaa, 1992; Massai, et al., 2001)
	Vaginal Ring	0.050	0.1-0.13	15 days – 6 months	(Brache, et al., 2001; Fraser, et al., 2005; Massai, et al., 2000)
		0.150 (+ 0.015 EE)	0.3-0.4	21 days – 25 weeks	(Fraser, et al., 2005; Sivin, et al., 2005)
		0.100	0.13	15 days	(Massai, et al., 2000)
		0.200	1.9-3.3	3.5 hours	(Jensen, et al., 2018)
DRSP	Oral	3 (+ 0.020 EE)	2-298	2.5 hours	(Blode, et al., 2001; Blode, et al., 2012; Wiesinger, et al., 2015)
DNG	Oral	2	151-182	1 hour	(McCormack, 2010; Shin, et al., 2013)
		2 (+ 0.030 EE)	73.9-206	1-3 hours	(Bayer Healthcare Pharmaceuticals Inc, 2010b; Carol, 1991; Foster & Wilde, 1998; Oettel, 1995; Perez-Campos, 2010; Zimmermann, 1999)
		2 (+ 2 E_2V)	172	1 hour	(Wellington & Perry, 2002; Zimmerman, et al., 2000)
CPA	Oral	2 (+ 0.050 EE)	35.5-54	3-4 hours	(Humpel, 1977)
NoMAc	Oral	2.5 (+ 1.5 E_2)	19.5-33.2	1.5-3.3 hours	(Gerrits, et al., 2013; Mueck & Sitruk-Ware, 2011)

*Reported C_{max} values were measured at different time points and using various methods.

#The concentrations at 1 year for long-term contraceptives are 0.434-0.864 nM (LNG IUD), 0.509-1.605 nM (LNG 75 mg implant), 0.618-1.986 nM (LNG 36 mg implant), 0.54-0.837 nM (ETG implant) and 0.06-0.221 nM (NES implant).

Data are summarized from detailed tables of published concentrations, available at Mendeley Data (http://dx.doi.org/10.17632/5sck77c9b9.1).