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METHODOLOGICAL CONTRIBUTIONS

Not All Progestins are Created Equally: Considering Unique Progestins Individually in Psychobehavioral Research

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Abstract

Objectives Progestins (i.e., synthetic progesterone) used in hormonal contraceptives (HCs) have been developed to mimic endogenous progesterone to inhibit ovulation and prevent pregnancy. Although the physiological side effects of different progestin formulations and administrative routes (e.g., oral pill, injection, skin patch) are well understood, the potential affective and behavioral side effects of various progestins are relatively under-studied. Progestins vary in terms of their dosage, bioavailability, metabolism, and affinity for progesterone and other steroid hormone receptors. Yet, research investigating the effects of these compounds on women's affect, sex drive, and mate preferences has not systematically accounted for these differences when considering their psychobehavioral side effects.
Methods Here, the biological differences between progesterone and progestins, as well as the differences between progestin types, are considered.
Results Research looking at the effects of progesterone and progestins on women's affect, sex drive, and mating psychology is reviewed, with emphasis on work that has explored differences between progestin types. In this review, we argue that accounting for these unique aspects of progestins is necessary for a comprehensive understanding of the influence of HCs on women.
Conclusion A better understanding of these differences may clarify previous research and inform future studies.

Keywords Hormonal contraceptives · Synthetic hormones · Progesterone · Progestin · Menstrual cycle · Mate preferences · Mood · Affect · Sex drive

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Worldwide, over 100 million women use a hormonal contraceptive (HC; e.g., oral pill, injection, hormonal intrauterine device, implant; Petitti 2003). HCs have changed the role that women play in the economy and their trajectory in the workforce by altering their career prospects, age at first marriage, and the age at which the average woman first gives birth (for a review, see Bailey 2006; Goldin and Katz 2002). The introduction of HCs has been associated with increases in positive health outcomes for women (e.g., reduced rates of maternal death, endometrial and cervical cancer, ovarian cysts, and pelvic inflammatory disease; reviewed in Welling 2013) and their children (e.g., reduction in child mortality rates via increased inter-birth interval; Cleland et al. 2012). The physical side effects of HCs (e.g., increased risk for venous thromboembolism, myocardial infarction, and stroke; see Welling 2013, for review) have been studied extensively (though not without controversy; see Liao and Dollin 2012) since contraceptives were introduced. However, the psychological and behavioral effects of HCs have only come into similar consideration relatively recently (Alvergne and Lummaa 2010; Hahn and Cobey 2019; Skovlund et al. 2016; Welling 2013), documenting effects of sex steroids on various behavioral domains in both non-human animals (e.g., Becker and Koob 2016; Drossopoulou et al. 2004; Johnston and File 1991) and humans. For example, HCs influence women's cognition (Pletzer and Kerschbaum 2014), affect (e.g., Donner and Lowry 2013; Kudielka and Kirschbaum, 2005; Skovlund et al. 2016), and behavior (reviewed in Hahn and Cobey 2019; Welling 2013) in ways that are not necessarily analogous to endogenous progesterone.

Progesterone is so named because it was first understood as a hormone that was vital to preparing the body for and maintaining pregnancy (i.e., it is pro-gestational), although it is now known to also have a number of other important effects on both men and women (e.g., acting as a neuroprotective agent after central nervous system trauma; Roof and Hall 2000). Progesterone is important for the development and maintenance of the uterine endometrium in preparation for and during pregnancy. At the beginning of a given menstrual cycle (the first day of menses onset), estrogen is increasingly released from the ovaries and is negatively feeding back to the anterior pituitary and reducing luteinizing hormone release, and progesterone levels are relatively low (Sherman and Korenman 1975). During this time, an ovum is developing in an ovarian follicle. After approximately one week of this gradual increase in estrogen, estrogen secretion rises dramatically. Estrogen then switches from a negative feedback signal to a positive one, which causes a sudden surge of luteinizing hormone (LH) to be released from the anterior pituitary. This surge of LH induces the release of a mature oocyte from the ovary, which is known as ovulation. There is also an increase in testosterone as the cycle approaches ovulation from ovarian thecal cells, which surround the estrogen-producing granulosa cells encircling the ovarian follicles. After ovulation, the site of the rupture of the dominant ovarian follicle transforms into a corpus luteum, which begins to secrete large amounts of progesterone that causes the uterine lining to proliferate in preparation for blastocyst implantation. Thus, progesterone is relatively low during the follicular phase, increases slightly just prior to ovulation, and begins increasing drastically following ovulation in the luteal phase (Sherman and Korenman 1975). Progesterone peaks around the middle of the luteal phase (during which time progesterone is higher than estradiol). If a fertilized embryo does not implant, the corpus luteum degenerates, hormone levels drop, and menses is

triggered, beginning the cycle again. Specifically, if a fertilized egg does not implant in the developing endometrium, declining luteinizing hormone levels signal the corpus luteum to degenerate and the developing endometrium is discarded (i.e., menstruation occurs). However, if a fertilized egg does implant, the corpus luteum will continue to secrete high levels of progesterone throughout the first trimester of pregnancy until the placenta assumes dominant progesterone production and secretion. During this process, progesterone level varies substantially across the cycle, across different cycles within the same individual, and between women (Jasienska and Jasienska 2008).

HCs, which contain a progestin (i.e., synthetic progesterone) and sometimes a synthetic estrogen (usually ethinyl estradiol), are used to prevent pregnancy, but also offer other health benefits, such as reduced menstrual flow, regulating menstrual cycles, and the reduction of other hormone-related symptoms (e.g., acne; Schindler 2013). HCs are available in several administration routes (e.g., oral pill, injection, hormonal IUD, skin patch) and hormonal formulations. Most provide a synthetic progestin at levels that inhibit the luteinizing hormone surge at mid-cycle, thus preventing ovulation. Inhibition of ovulation by HCs is clearly caused by effects on the central nervous system (i.e., the effects that estradiol and progestins have on the hypothalamus and the subsequent prevention of hormonal cascades that trigger follicle development and ovulation), although outside of these interactions, the effects that various progestins have on the central nervous system is still not well understood (for a review of effects of HCs on the central nervous system, see Pletzer and Kerschbaum 2014). Other forms of HCs, such as low-dose, progestin-only contraceptive pills and hormonal IUDs, less reliably control ovulation. Rather, they alter cervical mucus and endometrial lining in such a way that reduces the likelihood of pregnancy (Rivera et al. 1999).

The first HC approved in the United States, *Enovid*, was approved for regulation of menstrual cycles in 1957 and for contraceptive use in 1961 (although it was not approved for prescription to non-married women for another 10 years; Dohnt 2010). *Enovid* differs markedly from its modern counterparts, as it supplied roughly 10 mg of the progestin norethynodrel and 150 μg of the estrogen mestranol, whereas modern oral contraceptives supply estrogen doses in the range of 20–50 μg (e.g., *Ortho Tri-Cyclin*, *Ortho-Cyclen*, *Sprintec* [all 35 μg]) and a progestin component in the range of .1–3.0 mg (e.g., *Ortho Tri-Cyclin* [.18–.25 mg], *Yaz* [3 mg], *Ortho-Cyclen* [.25 mg]). Severe side effects (e.g., death from venous thromboembolism) were observed in users of *Enovid*, and its use was eventually discontinued. There has since been a directed effort to develop synthetic progestins with reduced side effects that more accurately mimic endogenous progesterone (Sitruk-Ware and Nath 2010), and many distinct progestin compounds have entered the market.

Research outside of the clinical realm has investigated the psychobehavioral effects of endogenous and synthetic hormones (e.g., on women's mate preferences for opposite-sex partners; Feinberg et al. 2008; Jones et al. 2005a, b), but much of this work has largely ignored the potential for different progestins to produce unique or nuanced effects based on their pharmacology and pharmacokinetics (although see Grøntvedt et al. 2017). Work investigating the effects of contraceptives on sexual behavior and mood has more quantitatively controlled for these differences, either by comparing contraceptive types within studies (e.g., Guida et al. 2005; Sabatini and Cagiano 2006) or by specifically recruiting participants who are using a single type of progestin (Caruso et al. 2004). Conversely, however, this work has largely ignored

ways in which the neuroendocrine system has been shaped by natural selection to modulate aspects of emotional, social, and reproductive behavior. Still, the effects of synthetic estradiol and progestins are not well understood in these contexts (for reviews, see Burrows et al. 2012; Pastor et al. 2013). Disambiguating how HCs function is vital for researchers interested in how synthetic hormones differ from their endogenous counterparts. There appears to be some confusion about how HCs function even among researchers who examine differences between women using HCs and those who do not (see Sprengelmeyer et al. 2009 and response from Fleischman et al. 2010). It is a common misperception that HCs elevate progesterone levels, when progestin use systematically reduces the biosynthesis of both progesterone, as well as other sex steroids, like estrogen and testosterone (Fleischman et al. 2010; Louw-du Toit et al. 2017).

The current review

The purpose of this review is to underline the need for considering dose, administrative route, and progestin type when investigating psychobehavioral effects of HCs. Below, we provide an overview of how endogenous progesterone functions biologically and review the biological functions of various synthetic progestins, with special attention to differences between unique progestins and between progestins and progesterone, with an emphasis on the adaptive role progesterone plays in coordinating systems important for social behaviors and bonding (e.g., mood and affect systems, sexual drive and mating systems). An overview of literature documenting how HCs have been linked to changes in affect, sex drive, and mate preferences compared to endogenous progesterone will follow, with emphasis on studies that have quantified differences between progestin types. Although synthetic estrogen, an important component of many HCs, has also been associated with changes in women's mood (Best et al. 1992) and behavior (Cobey et al. 2012; Grøntvedt et al. 2017; Welling et al. 2012), most HCs approved for use contain ethinyl estradiol. Due to this similarity and the breadth of different progestins contained in various contraceptives, this review focuses on synthetic progestins.

Biological characteristics of endogenous progesteronehj

Progesterone's biological and psychological effects are determined by the biological availability of the hormone, the number and distribution of progesterone receptor (PR) types in specific tissues, and the presence of other potential binding hormone sites. Progesterone is a steroid hormone derived from cholesterol that is synthesized in luteal cells (Niswender 2002), as well as in the central and peripheral nervous system as a "neurosteroid" (i.e., steroids synthesized within the nervous system that modulate the activity and excitability of neurotransmitter receptors; Baulieu 1997). The biological activity of progesterone is mainly determined by the amount of bound and unbound hormone in circulation and the local availability of PRs to which progesterone can bind.

Progesterone is sensitive to metabolism when freely circulating in plasma and circulates bound to the serum protein transcortin (also referred to as cortisol binding

globulin [CBG]; e.g., Westohal 1986) and has a moderately high affinity for the serum protein albumin. Progesterone not bound by serum proteins is referred to as "free" progesterone (i.e., available to be metabolized, or "bioavailable"). Because serum proteins influence the availability of free progesterone, the quantity of serum proteins in circulation can control the amount of free progesterone. Its metabolism is tissue-specific, but it regularly undergoes enzymatic reduction and has several biologically active metabolites (e.g., allopregnanolone; Stanczyk 2003).

Steroid hormones act on cells via either genomic or non-genomic pathways. They interact with intracellular cognate receptors to form a ligand-receptor complex, which can then act as a transcription factor (Falkenstein et al. 2000). Via the association with the PR, progesterone influences genomic expression (e.g., Richer et al. 2002; Robker et al. 2000). There are two main nuclear PRs: progesterone receptor-A isoform (PRA) and progesterone receptor-B isoform (PRB). PRA and PRB are alternative splice variants of a single gene (Conneely et al. 1987) and have distinctive cellular functions (e.g., Mulac-Jericevic et al. 2000; Richer et al., 2002). In other words, progesterone has different effects on gene expression when it is bound to PRA versus PRB (for review, see Li and O'Malley 2003). Recent evidence has shown that cell-membrane associated PRs (i.e., membrane progestin receptor alpha and progesterone membrane receptor component 1 [PGMRC-1]; Thomas 2008) influence important transduction pathways (e.g., interactions with G protein-coupled receptors; Burger et al. 1999) and that progesterone has effects on the cell outside of its interaction with nuclear receptors (i.e., non-genomic effects).

Progesterone and its metabolites also interact, at least *in vitro*, with other steroid hormone receptors, specifically the mineralocorticoid (MR; e.g., Quinkler et al. 2002) and glucocorticoid (GR; e.g., Lei et al. 2012) receptors. Interactions with other receptors may lead to transactivation (i.e., an increase in gene transcription caused by ligand-activated steroid receptors binding to response elements on the promoters of target genes) or to transupression (i.e., decrease in gene expression due to ligand-bound receptors interacting with other transcription factors). As a neurosteroid, progesterone allosterically modulates (i.e., interacts with a receptor at a site separate from the primary [orthosteric] site) both the oxytocin receptor and, through its metabolite allopregnanolone, the GABA-A receptor (Edwards 2005).

Biological characteristics of synthetic progestins

A fully comprehensive review of how chemical structures of progestins differ from endogenous progesterone is beyond the scope of this article (for review, see Schindler et al. 2008; Stanczyk 2003). It is, however, necessary to briefly review key differences in progestins to better understand why their biological activity (e.g., potency, pharmacokinetics) differs from one another and to highlight some of the differences compared to endogenous progesterone. There are two broad categories of synthetic progestins: (1) compounds structurally related to progesterone and (2) compounds structurally related to testosterone. This classification scheme is indicative of the structural *similarities* between progestin compounds and other steroid hormones and does not indicate how a specific progestin was derived (i.e., it does not refer to the parent molecule

used for derivation). These structural similarities are informative when we consider how progestins interact with other steroid hormone receptors and plasma carrier proteins.

Progestins structurally related to progesterone can be divided into pregnanes and 19-norpregnanes. An example of a pregnane is medroxyprogesterone acetate (MPA), which is commonly used for hormonal replacement therapy (HRT) and also comes in an injectable form (depo-medroxyprogesterone acetate; DMPA). Nineteen-norpregnanes include nomegestrol acetate and nestorone. Progestins structurally related to testosterone can be divided into estranes and gonanes (i.e., 13-ethylgonanes). Estranes include norethisterone (also known as norethindrone) and norethisterone acetate, whereas gonanes/13-ethylgonanes include levonorgestrel, desogestrel, gestodene, and norgestimate. Finally, a newer progestin, drospirenone, is a spironolactone derivative. Spironolactone is an aldosterone antagonist and drospirenone is an analogue that has unique progestational capacities (Krattenmacher 2000). Progestins contained within the same class have unique biological activity compared to one another (Stanczyk et al. 2013), and considering progestins separately rather than grouping them by class may yield the most fruitful insight into their specific effects.

Circulation, metabolism, and bioavailability of progestins

Progestins have varying affinities for CBG and albumin (see Schindler et al. 2008). Additionally, some progestins will bind to other plasma carrier proteins, such as sex hormone binding globulin (SHBG), which can influence the quantity of available estrogen and testosterone because SHBG is the carrier of these steroid hormones. Unlike progesterone, synthetic progestins do not show any binding affinity for CBG (see Schindler 2013). Rather, many progestins circulate bound to albumin (e.g., medroxyprogesterone acetate, megestrol acetate). Progestins structurally related to testosterone (e.g., norethisterone, levonorgestrel, gestodene) bind to SHBG and albumin. Cortisol, the main steroid hormone that CBG binds to in plasma, may be affected by these differences because available CBG determines plasma cortisol levels (Bolton et al. 2014). Synthetic hormones reduce the quantity of endogenous sex steroids that the body produces *de novo* (Louw-du Toit et al. 2016; Louw-du Toit et al. 2017). With a reduced level of progesterone and a synthetic molecule that does not bind to CBG, there is more CBG available to bind to cortisol, thus potentially reducing the quantity of free cortisol and/or up-regulating the quantity of cortisol produced. Furthermore, increased estradiol level has been associated with an increase in CBG production, and therefore higher doses of estradiol in HCs may also influence CBG production (Wiegratz et al. 2003). These differences in CBG availability and cortisol production may be reflected in studies that have found HC users have different cortisol awakening responses (e.g., Bouma et al. 2009) and different responses to stress compared to naturally cycling women (e.g., Gaffey et al. 2014; Kirschbaum et al. 1999; Nielsen et al. 2014), suggesting that HCs influence the hypothalamic-pituitary-adrenal (HPA) axis.

Progestins have unique effects on the production and availability of SHBG. Progestins structurally related to testosterone have a moderate affinity for SHBG and can displace testosterone from SHBG, resulting in higher bioavailable quantities of this

androgen. However, it appears that all progestins increase the production of SHBG, although gonanes less so than estranes or progestins structurally related to progesterone (Zimmerman et al. 2014). Any increase in the availability of testosterone that gonanes may provide via competitively binding with SHBG appears to be inconsequential when considering the relative increase in SHBG and reduction of biosynthesis of testosterone caused by all progestins. The reduction of bioavailable testosterone may be linked to reports of reduced sex drive and sexual functioning that some women report when using HCs (Burrows et al. 2012; Pastor et al. 2013).

Endogenous progesterone is readily metabolized when given orally and synthetic progestins intended to be taken orally have been designed to survive first-pass hepatic metabolism and are mainly metabolized by the liver (Stanczyk 2003), whereas other progestins that are parenterally administered (i.e., internally, such as in an IUD, vaginal ring, or intramuscular injection) are first metabolized by the tissues nearest the site of administration (for a comprehensive review of the metabolic pathways and potential metabolites of different progestin compounds, see Kuhl 2005). Upon metabolism, some progestins, such as norethindrone, are converted to ethinyl estradiol, which can increase the dosage of estradiol that users experience. Relatively little research has investigated the metabolism and potentially biologically active metabolites of progestins, and there is not much known about the metabolism of some of the most widely used progestins (e.g., medroxyprogesterone acetate; Stanczyk et al. 2013). There are multiple different metabolites formed from each progestin and these could result in different biological outcomes. Endogenous progesterone is metabolized into several biologically active compounds (e.g., allopregnanolone), and it may be important for future drug developers to consider these aspects when designing new progestin compounds.

The absolute quantity of bioavailable progestin depends on the method of administration, dosage, and pharmacokinetics (i.e., absorption, distribution, and excretion) of each individual compound (see Kuhl 2005 and Stanczyk et al. 2013 for reviews of pharmacokinetics of individual progestins). For progestins taken orally, the maximum quantity of bioavailable drug is reached within 1–3 h after ingestion, and plasma levels decrease after that point in a manner that is dependent on the half-life (the amount of time it takes for one half of the administered dose to be metabolized) of each progestin compound. Although progestin levels are kept at an average level that prevents ovulation, serum progestin levels vary between the time each pill is consumed. Certain progestins taken orally have a higher bioavailability because they are not metabolized in the gut. Alternatively, progestins contained in vaginal rings reach peak serum concentration after one week of initial administration (Timmer and Mulders 2000) and result in relatively constant serum levels of progestin. Medical implants, injections, and intrauterine devices display a similar pattern of hormone release, although over different time periods. For example, implants and IUDs result in higher average hormone levels during the first year from the time of administration, with hormone levels steadily tapering off before removal. These methods of administration lead to differing levels of circulating hormones, but exhibit more steady serum concentrations than progestins taken orally.

Activity of progestins on the progesterone receptor and other steroid receptors

Progestins were originally designed to mimic the effects of progesterone on the PR to subvert and arrest the ovulatory cycle. However, since the development of the first progestins, what is known about the complex role that progesterone plays in a plethora of reproductive and non-reproductive capacities has expanded. Like progesterone, progestins also interact with other steroid hormone receptors aside from PR (see Table 1 for breakdown of different biological activity of various progestins). All progestins show affinity for the human PR to varying degrees and are PR agonists (Stanczyk et al. 2013). The affinity with which progestins bind to steroid receptors is biologically significant in that cellular responses to progestins depend in part on their concentration and how competitively they bind with receptors compared to other ligands. These factors determine receptor occupancy, which in turn influences biological response, such as DNA transcription. In terms of binding affinity, there are a number of progestins that exhibit a stronger affinity for human PR compared to progesterone. In descending rank order for PR receptor affinity, gestodene, trimegestone, levonorgestrel, medroxyprogesterone acetate, and norethisterone have higher binding affinity for the human PR compared to progesterone (Africander et al. 2011; Attardi et al. 2010). Two newer progestins, drospirenone and dienogest, have weaker affinity for the PR receptor compared to progesterone. It is difficult to compare affinity values from various studies because these depend on the tissue type, cell line, and other experiment-specific factors. Little research has been done addressing the effects of progestins on the different progesterone receptor isoforms, although it is likely that progestins have different affinities for PRA and PRB based on their structural similarities to progesterone or testosterone (Africander et al. 2011). In addition to PRA and PRB, how progestins interact with membrane-bound progesterone receptors is unknown, although some early evidence suggests that norethisterone does bind to a progesterone membrane receptor (Thomas et al. 2007).

Many progestins also interact with the androgen (AR), mineralocorticoid (MR), and glucocorticoid (GR) receptors (Attardi et al. 2010; Losert et al. 1985; Regidor and Schindler 2017; Sitruk-Ware 2003; Stanczyk et al. 2013). More recent progestins were designed to reduce some of the unwanted side effects of earlier generations (e.g., bloat, weight gain, skin problems), which were likely driven by the effects that these compounds had on off-target steroid receptors (Hapgood et al. 2004; Regidor and Schindler 2017). When discussing affinity for a receptor, this does not imply that progesterone or progestins activate the receptor as a natural ligand would. These interactions may result in agonistic, partially agonistic, or antagonistic effects. Older progestins, such as medroxyprogesterone acetate, levonorgestrel, and norethisterone, are androgen receptor agonists and do not display anti-androgenic activity, whereas newer progestins, such as drospirenone, dienogest, and trimegestone, have strong anti-androgenic effects and have no agonist activity at the AR (e.g., Louw-du Toit et al. 2017). Others, such as nestorone, do not appear to interact with the AR (e.g., Kumar et al. 2016). Differences in the androgenic nature of progestins may result in specific side effects. For example, women using anti-androgenic progestins have a decrease in skin issues such as acne, which are undesirable side effects of some androgenic progestins (Sitruk-Ware and Nath 2010).

Table 1 Relative biological actions of various progestins categorized by chemical structure

Category	Progestin	Progestogenic	Androgenic	Anti-Androgenic	Estrogenic	Anti-Estrogenic	Anti-Mineralocorticoid	Glucocorticoid
	Progesterone	+	−	+	−	+	+	+
Pregnanes								
	Medroxyprogesterone acetate	++	+	−	−	+	−	+
	Megestrol acetate	+	±	+	−	+	−	+
	Cyproterone acetate	+	−	++	−	+	−	+
Norpregnanes								
	Gestodene	+	−	±	−	+	+	±
	Nomogesterol acetate	++	−	+	−	+	−	−
	Nesterone	+	−	−	−	+	(?)	−
	Trimegestone	++	−	−/+	−	+	+	−
	Promegestone	+	−	−	−	+	−	−
Estranes								
	Norethisterone	+	+	−	+	+	−	−
	Norethinodrel	±	±	−	+	±	−	−
Gonanes								
	Levonorgestrel	++	+	−	−	+	−	−
	Desogrestrel	++	+	−	−	+	−	−
	Gestodene	+	+	−	−	+	+	±
	Norgestimate	+	+	−	−	+	−	−
	Dienogest	+	−	+	±	±	−	−
Spironolactone derivative								

Table 1 (continued)

Category	Progestin	Progestogenic	Androgenic	Anti-Androgenic	Estrogenic	Anti-Estrogenic	Anti-Mineralocorticoid	Glucocorticoid
	Drospirenone	++	–	+	–	+	+	–

Although all progestins display activity at the progesterone receptor and are to varying degrees progestogenic, they differ in their effects at other steroid receptors, such as the estrogen and testosterone receptors. (+) = weakly effective, (++) = strongly effective, (−) = not effective, (±) = literature regarding interaction is not consistent, (?) = no literature defining interaction. Data adapted from Kuhl (2011), Louw-du Toit et al. 2017, Schindler et al. (2008), Sitruk-Ware (2005), and Stanczyk et al. (2013)

Progesterone interacts with the MR and may be a competitive antagonist for MR ligands, such as aldosterone, when progesterone levels are particularly elevated (e.g., during the luteal phase and during pregnancy). Although the physiological implications of these interactions *in vivo* are not fully understood, MRs are expressed in brain regions important for emotional memory formation (Joëls and Baram 2009), and it is possible that progesterone has modulatory capacities in this realm via the MR (Hamstra et al. 2017). Progestins have varying capacities for binding at the MR. Some newer progestins, such as drospirenone and trimegestone, were specifically developed to have anti-mineralocorticoid properties because these were theorized to have benefits for reducing blood pressure and improving cardiovascular function (Stanczyk et al. 2013). Progesterone has a weak affinity for the GR, which is ubiquitously expressed, whereas progestins have diverse affinities and effects at this receptor. For example, Koubovec et al. (2005) found that medroxyprogesterone acetate had stronger affinity for the human GR than progesterone and was a stronger agonist than norethisterone acetate or progesterone. Medroxyprogesterone acetate and megestrol acetate have shown a high affinity for the GR receptor, and these progestins are likely to have side effects related to their GR activity (e.g., Kontula et al. 1983; Koubovec et al. 2005), potentially compromising immune and cardiovascular function.

Anxiety and mood

One area of research that highlights the need for the separate consideration of the effects of different progestins comes from work investigating the role of progesterone, allopregnanolone, and progestins on women's anxiety and mood. Progesterone and its metabolite allopregnanolone can induce anxiolytic-like behavior and reduce depressive-like behavior (e.g., immobility during a forced-swim test) in rats, and these changes are linked to the availability of allopregnanolone in the hippocampus (Frye and Walf 2002). However, the effect of progesterone on anxiety in humans is not as clear. An anxiolytic, sedative-like effect of exogenous progesterone administration has been observed in humans (Freeman et al. 1993; Söderpalm et al. 2004), but women with higher average levels of endogenous progesterone across their menstrual cycle report higher anxiety than women with lower average levels, and rising levels of progesterone across the menstrual cycle is positively associated with reported attachment anxiety (Reynolds et al. 2018). Endogenous progesterone and allopregnanolone are also stress-responsive in humans, such that after experiencing a stressful event, men's and women's bodies produce and release progesterone and allopregnanolone (although these responses appear to be menstrual-phase specific in women; see Wirth 2011, for review). The observed anxiolytic effects of progesterone may be mediated by the effects of allopregnanolone on the amygdala (Sripada et al. 2013).

Progesterone and allopregnanolone are also associated with premenstrual dysphoric disorder (PMDD), which manifests during the second half of the menstrual cycle (i.e., the luteal phase), and causes symptoms of depression, anxiety, and mood swings (Halbreich et al. 2003). The evidence that progesterone levels, *per se*, are associated with PMDD is mixed; some studies have found that higher levels of progesterone during the luteal phase are associated with an increase in PMDD-related anxiety and depression, whereas others have found a negative or null relationship (reviewed in

Bäckström et al. 2003). Some research has found that the conversion of progesterone to allopregnanolone may be altered in women with PMDD, and an increase of allopregnanolone during the luteal phase could be linked to an increase in experience of anxiety symptoms in women who have PMDD (Girdler et al. 2001). It may be that progesterone or allopregnanolone dysregulation, rather than strictly higher or lower levels, may account for PMDD symptoms via the paradoxical effects of positive GABA modulators in a subset of the population (for a review, see Bäckström et al. 2014). Other research has found that a specific kinetic profile of progesterone during the end of menstrual cycles (close to onset of menses) is related to the experience of premenstrual symptoms, such that women who experience a rapid drop in progesterone levels three days before the onset of menstruation experience perimenstrual syndrome (PMS) symptoms, whereas women who experienced a more gradual decline in progesterone levels during the eight days prior to menstrual onset do not (Lovick et al. 2017).

As mentioned above, some research shows that both progesterone and allopregnanolone are stress-responsive in humans. This increase in progesterone in response to stressors may be an adaptive response that influences individuals to seek social contact with others, potentially to reduce the negative effects of stress (e.g., Maner et al. 2010). In other words, progesterone may moderate how individuals seek social closeness to cope with and manage feelings of anxiety or depression. For example, progesterone increases in response to social closeness in humans (Brown et al. 2009) is positively associated with implicit affiliation motives (Schultheiss et al. 2003; Wirth and Schultheiss 2006) and appears to differentially respond to social rejection in women based on individual social motives (Maner et al. 2010). There are a number of ways that individuals can respond to interpersonal rejection or exclusion: social withdrawal, which protects people from further risk of ostracism, aggression and antagonism, to potentially reassert themselves, or a heightened desire to seek out social contact. Maner et al. (2010) found that women who were higher in social anxiety displayed a drop in progesterone following social exclusion, whereas women who were low in social anxiety had an increase in progesterone. The same pattern was also observed based on social rejection sensitivity (i.e., how likely an individual is to perceive social rejection), suggesting that progesterone secretion in response to social rejection is linked to individuals' social motivations. It has further been theorized that progesterone is related to depression in that reduced levels of progesterone and allopregnanolone are observed in patients with these disorders and may influence social withdrawal (Wirth 2011).

Progesterone also influences social perception in ways that are associated with its effects on mood and anxiety. Progesterone has been linked to specific facets of emotional learning and memory; in particular, it appears to be positively related to how well emotional memories are encoded (Ertman et al. 2011) and to amygdala activation in response to negative imagery (Petersen and Cahill 2015). Maner and Miller (2014) found that estimated progesterone levels were associated with greater accuracy in identifying emotional facial expressions and actual progesterone levels were associated with greater attention to social, but not non-social, stimuli in a dot-probe task. These studies suggest that progesterone helps to adjust women's perception of their environment in adaptive ways. These changes may be adaptive if we consider that progesterone levels increase when women's bodies are preparing for pregnancy,

and that progesterone levels remain elevated during pregnancy. An increase in progesterone may signal women to alter their social behavior in ways that would be beneficial in case of pregnancy, perhaps by helping them avoid social threats and recruit potential friends and allies during a time when stable resource availability is important (Maner and Miller 2014).

Previous research has found that, unlike in women who are naturally cycling, progesterone levels are not associated with affiliation motives in women using HCs (Schultheiss et al. 2003). Furthermore, women who are using HCs do not show an increase in attention to social stimuli over the menstrual cycle like naturally cycling women do during the luteal phase (Maner and Miller 2014). Recent research has indicated that mineralocorticoid receptor haplotype may influence the impact of HCs on processing emotional imagery; HC users possessing mineralocorticoid receptor haplotypes 1 and 3 are more perceptive of fearful and sad faces than HC users possessing mineralocorticoid receptor haplotype 2 (Hamstra et al. 2016; Hamstra et al. 2017). A recent meta-analysis also concluded that women using HCs had impaired facial emotional processing compared to naturally cycling women (Osório et al. 2018). It is possible these findings represent a dysregulation in regions of the brain that are important for emotional processing and emotional regulation, and that this dysregulation is what makes women using HCs more susceptible to developing a mood disorder (Montoya and Bos 2017).

One of the most often cited reasons for ceasing to use a HC is adverse side effects, one of which is worsening of mood (Rosenberg et al. 1995; Sanders et al. 2001). Paradoxically, one of the FDA-approved methods of treating PMDD is with contraceptives containing drospirenone (Cunningham et al. 2009). In a double-blind, placebo-controlled crossover study, treatment with drospirenone was better than placebo at reducing symptoms associated with PMDD (Pearlstein et al. 2005). Although considered to be one of the non-contraceptive benefits of HCs (Schindler 2013) and although many clinicians use HCs to manage PMS symptoms, previous research investigating the specific effects of progestins (aside from drospirenone) on PMS symptoms have shown only small differences (Yonkers et al. 2017), null effects, or a negative relationship (i.e., progestin use was associated with an increase in PMS-related symptoms; Bäckström et al. 2003; Usman et al. 2008). It is possible that the specific anti-mineralocorticoid and anti-androgenic effects of drospirenone are responsible for its unique effects on PMDD and PMS-related mood symptoms (Yonkers et al. 2008). These conflicting results may point toward person-specific factors that predispose certain individuals to be sensitive to the mood effects of HCs or specific progestins. Comparisons of drospirenone with other progestins that vary in their anti-mineralocorticoid and anti-androgenic effects may help elucidate drospirenone's distinct effects on PMDD and PMS symptoms. The role that different progestins play in modulating allopregnanolone levels should also be considered, as some progestins have been shown to decrease and stabilize endogenous allopregnanolone levels (e.g., Porcu et al. 2012; Santoru et al., 2014). This effect may be beneficial for individuals who are particularly sensitive to high or fluctuating levels of allopregnanolone, but could result in the development of mood or anxiety symptoms in those who are less sensitive to changes in GABA modulators or whose allopregnanolone levels are reduced too greatly by HC use.

Other research has found that women using oral contraceptives have less variability in affect and mood across cycles compared to women who are not using HCs (Oinonen

and Mazmanian 2002). These authors also found that monophasic formulations (i.e., contraceptives that contain the same quantity of progestin and/or estradiol across the cycle) resulted in more mood stability than triphasic formulations (i.e., contraceptives that vary in progestin dosage across weeks leading to the placebo/withdrawal period week), which may implicate progestins in the increase in mood stability. This type of research design highlights the necessity of investigating dosage effects of synthetic hormones on target behaviors and the unique effects of different contraceptive formulations (i.e., monophasic, biphasic, triphasic, continuous). However, it should also be noted that many studies investigating the influence of HCs on mood may be influenced by the survivor effect (e.g., Kay 1984). Individuals who experience negative side effects while using contraceptives are more likely to discontinue use and may become less represented in studies that sample women who have been using contraceptives for longer periods of time.

In an impressive recent study including over one million Danish women, Skovlund et al. (2016) investigated how incident rates ratios for a first use of antidepressant and for first diagnosis of depression was associated with use of various forms and formulations of HCs. They found that use of HCs, especially in young women, was associated with a higher incidence of both prescription of antidepressants and of a depression diagnosis, even after removing women who had been diagnosed with any major psychological disorder (including depression) before their 15th birthday. These authors found that the use of specific forms of HCs containing different progestins was associated with different incidence rates (i.e., the number of new reported cases in a given population) of an antidepressant prescription. Women using progestin-only pills, as well as women using the patch (norestrolmin) and the vaginal ring (etonogestrel), had higher incident ratios for antidepressant use compared to women who did not use contraceptives. Women in these groups also had higher incident rates than women using other forms of progestins, such as a combination ethinyl estradiol and norethisterone oral pill. In a more recent study, the same group also found that women using specific forms of contraceptives (e.g., vaginal ring) were at higher risk for suicide attempt relative to non-users and users of other types of contraceptives (Skovlund et al. 2017). The results of these studies are particularly compelling and emphasize the specific ways that different progestins contribute to the development of mood disorders. Further replications of this research and an expansive consideration of how separate progestins contribute to the experience of depressive symptoms and changes in affect is a topic that deserves more inquiry.

Sex drive and sexual functioning

Another body of research has implicated both steroid hormones and progestin use to changes in women's sexual drive and functioning. Sex drive is positively associated with androgens in women, although the precise androgen (e.g., total or free testosterone, androstenedione, or dehydroepiandrosterone sulfate) is debated (see Davis et al. 2005). Evidence for the relationship between androgens and sex drive comes from a substantial body of literature documenting ways in which various androgens, particularly testosterone, influence women's sex drive. For example, pre-menopausal women with low sex drive and poor physiological function have an increase in sexual function

after testosterone treatment (Goldstat et al. 2003), and testosterone administration in post-menopausal women has been used as a treatment for hypoactive sexual desire disorder (e.g., Braunstein et al. 2005; Buster et al. 2005). A combination of androgens (e.g., free testosterone and androstenedione) are positively correlated with women's sex drive (Wåhlin-Jacobsen et al. 2015, 2017), and decreased androgen levels are associated with lower sexual desire, arousal, lubrication, and orgasm scores (Turna et al. 2005). Despite evidence for supraphysiological elevations of testosterone increasing women's sexual desire, some have argued that estradiol, rather than testosterone, is more reliably linked to sexual desire in women (Cappelletti and Wallen 2016). Certainly, in many other mammalian species estradiol has been found to be important for female sexual motivation (see Cappallet and Wallen 2016). There is evidence that elevated estradiol levels positively predict women's sexual desire during natural menstrual cycles (Shirazi et al. 2019), whereas some research finds that endogenous testosterone fluctuations across the cycle do not (Jones et al. 2018a; Roney and Simmons, 2013; but see Shirazi et al. 2019).

Sexual desire and motivation have also been linked to progesterone levels. Progesterone is negatively associated with sexual behavior in several non-human primates (Roney 2015; Wallen 2001). Changes in sexual behavior across women's menstrual cycle, such as an increase in women's sexual initiation (Adams et al. 1978) and sexual desire (Arslan et al. 2018; Roney and Simmons 2013) during the follicular phase, have linked sexual motivation to low progesterone. Among post-menopausal women receiving hormonal replacement therapy, "adding back" a synthetic progesterone component to hormonal therapies reduces their effectiveness at restoring sex drive (Dennerstein et al. 1980). Importantly, this research suggests that progestins may negatively influence sex drive through their own mechanisms or through the suppression of other hormones like androgens.

Aside from issues with mood, changes in sexual desire or sexual functioning ascribed to HC use is one of the other best predictors of women discontinuing use of HCs (Rosenberg et al. 1995; Sanders et al. 2001). Given that androgens are associated with women's sex drive (Wåhlin-Jacobsen et al. 2015, 2017), research investigating the effects of HC on sex drive have largely focused on the effect of HCs on endogenous androgens. Although all progestins reduce the biosynthesis of testosterone and other androgens and increase the production of SHBG (Zimmerman et al. 2014), which reduces the total quantity of androgens available in circulation, the use of progestins has not been found to reliably influence sex drive in all women in a specific direction (for review see Burrows et al. 2012; Casey et al. 2017; Pastor et al. 2013).

There are positive effects of HCs on women's sexual functioning, such as reduction of gynecological pain, and some studies suggest that drospirenone may be effective at treating some symptoms of endometriosis (Köhler et al. 2010). However, other studies have found that use of HCs is associated with negative changes in sexual desire and functioning (e.g., Smith et al. 2014; Wallwiener et al. 2010a; Wallwiener et al. 2010b). For instance, vaginal lubrication, which is influenced by circulating androgens, is negatively associated with HC use; users of two different oral contraceptives containing either levonorgestrel or gestodene experienced increased vaginal dryness (although these symptoms improved the more cycles women used the contraceptives; Sabatini and Cagiano,

2006). Van Lunsen et al. (2018) found that both oral contraceptive pills containing levonorgestrel and drospirenone reduced scores on desire for sexual partners, and levonorgestrel reduced arousal, lubrication, sexual arousability, whereas drospirenone did not. The addition of dehydroepiandrosterone (DHEA, an androgen) improved the facets of sexual functioning that were reduced by contraceptive use. Androgenic progestins may result in lesser reductions in sexual functioning, but, thus far, research testing whether switching from HCs containing anti-androgenic progestins to those containing androgenic progestin has not supported this idea (Davis et al. 2013). Two studies have found that use of combined oral contraceptives, irrespective of progestin type or dose, was associated with lower scores of sexual desire and arousal (Wallwiener et al. 2010a) and lower scores on measures of sexual function (Wallwiener et al. 2010b). Method of administration may also be associated with sexual function; one study found that depo-medroxyprogesterone (progestin-only injection), the vaginal ring (etonogestrel), and implant (etonogestrel) caused reductions in desire, whereas other contraceptive types did not (Boozalis et al. 2016). Decline in sexual desire across women's lifetime has been linked to declining estrogen levels and it has been suggested that these progestin-only contraceptive types may be reducing sex drive through their reduction in endogenous estrogen production and lack of synthetic replacement (Boozalis et al. 2016).

HCs may influence sexual satisfaction and function via other routes aside from modulation of endogenous hormone levels. Genetic factors, such as the number of polymorphisms in androgen receptors (which is related to reactivity/activity of androgen receptors) may also influence women's response to HCs (Elaut et al. 2012; Goldstein et al. 2014). Sexual desire and functioning are negatively associated with mood disorders and depression (Kennedy et al. 1999) and there is a strong connection between cognition and sexual functioning in women (Basson et al. 2003), such that disturbances in mood and affect can have reciprocal effects on sex drive and sexual functioning. Thus, the negative mood effects that women experience when using different progestins may also impact their sex drive and sexual functioning.

Despite decreases in sexual desire and functioning being a commonly reported unwanted side effect of HC use, there are few studies that systematically compare the effects of different progestin types, HC formulation, or HC administrative routes on women's sexual desire and functioning. Most comparative studies have focused on the effects of two or three varieties of progestins (e.g., van Lunsen et al. 2018; Sabatini and Cagiano, 2006), contraceptives types (e.g., comparison of oral HC users to non-oral routes of HC use; Wallwiener et al. 2010a), or grouped all HC users together and compared them to non-users (e.g., Smith et al. 2014). This approach fails to capture progestin, formulation, and route-specific effects of HCs on sexual functioning and drive. It is still unclear which factors make some women more susceptible to changes in sexual desire or functioning upon initiation of HCs. Future large-scale studies accounting for these factors, similar to the Skovlund et al. (2016, 2017) approach, are needed in this area of research, as sexual health and satisfaction have been linked to important life and relationship outcomes (e.g., relationship satisfaction, commitment, and stability; Sprecher 2002).

Mating preferences and relationship dynamics

Research addressing the effects of steroid hormones on women's mating preferences has flourished in the past 20 years, although not without contention (see Gangestad and Grebe 2015; Gildersleeve et al. 2014b; Havlíček et al. 2015; Roney et al. 2015; Wood et al. 2014). Just like women's mood and sex drive, women's preferences for opposite-sex morphological characteristics (e.g., facial sexual dimorphism, skin coloration, body morphology) and partner-directed behaviors (e.g., jealousy, mate retention behaviors) have been linked to changes in endogenous steroid hormones that fluctuate across the menstrual cycle (for review, see Gildersleeve et al. 2014a, 2014b; Welling and Burriss 2019; Welling 2013; but see Jones et al. 2018b; Jones et al. 2018c; Jünger et al. 2018b) and the use of HCs (see Alvergne and Lummaa 2010). Also similar to research on mood and sex drive, research considering the unique effects of different progestin types have been understudied in this body of literature (although see Grøntvedt et al. 2017). Particularly, this research has tended to group contraceptive users together, with the main constituents of the HC samples being individuals using various oral contraceptives.

When progesterone levels are elevated, women show an increase in preference for traits that are thought to be indicative of current health, such as facial skin coloration (Jones et al. 2005a, b), and higher preferences for facial femininity (Jones et al. 2005a; Puts 2006), which is associated with better long-term parental investment (Perrett et al. 1998). However, other studies have associated preference changes with other steroid hormones (e.g., Roney et al. 2011; Welling et al. 2007) or found no association with any steroid hormone (Jones et al. 2018a, 2018b). Marcinkowska et al. (2018) found an interaction between relationship status and hormonal status, such that women's average progesterone levels were negatively associated with facial masculinity preferences for women who were in committed relationships only (see also DeBruine et al. 2019). Progesterone is also negatively associated with women's preference for and perception of human facial symmetry (Little et al. 2007b; Oinonen and Mazmanian 2007), masculine male voices (Jünger et al. 2018b; Puts 2006; Shirazi et al. 2018), and masculine male bodies (Gangestad et al. in press; Jünger et al. 2018a; Little et al., 2007a; although see Peters et al. 2009).

There is growing literature documenting differences in women's mate preferences based on their use of HCs (reviewed in Hahn and Cobey 2019; Welling 2013). In terms of women's preference for opposite-sex characteristics, oral contraceptive users may have weaker preferences for men's facial and vocal masculinity and do not show a mid-cycle increase in preference for these traits, unlike naturally cycling women (Feinberg et al. 2008; Little et al. 2007a; Penton-Voak et al. 1999; although see Jones et al. 2018b). Some research has found that when women initiate oral contraceptive use that their preferences for male facial masculinity decrease (e.g., Little et al. 2013). Testosterone levels have also been associated with masculinity preferences in women (Welling et al. 2007). Bobst et al. (2014) found that testosterone levels during women's earlier follicular phase were predictive of preference for male facial masculinity, but only in women who were not using oral contraceptives. Oral contraceptives also increase women's preferences for cues to current health (e.g., skin coloration, skin texture; Jones et al. 2005b) and may alter women's ability to process specific components of faces, such as emotional expressions (Osório et al. 2018). Furthermore, women

using oral contraceptives do not show an increase in preference for masculine male bodies at mid-cycle (Little et al. 2007a). It is important to again note that the majority of the above studies and those described below have considered contraceptive users as a single, homogenous group and that participants in these studies have largely been using various forms of oral contraceptives.

There is also evidence that women's hormonal status influences how attractive they are considered by both men and women, as well as aspects of their interpersonal relationships (e.g., relationship satisfaction, jealousy, mate retention behavior). For instance, Miller et al. (2007) found that lap dancers in "gentleman's clubs" reported earning different tips depending on where they were in their menstrual cycle. Women who were naturally cycling received significantly more tips when they were in their follicular phase compared to their luteal phase, whereas women who were using HCs did not report changes in tips. Laboratory research has also found that the attractiveness of women's faces, voices, and scents varies cross the menstrual cycle in ways that are specifically related to progesterone, estrogen, and testosterone levels (e.g., Gildersleeve et al. 2012; Havlíček et al. 2006; Kuukasjärvi et al. 2004; Lobmaier et al. 2018). Ratings of women's vocal attractiveness are positively related to conception risk (Pipitone and Gallup Jr 2008), and progesterone negatively predicts attractiveness ratings of both women's faces and voices by men and women raters (Puts et al. 2013; Roberts et al. 2004). More recently, high-powered study found that progesterone and estrogen levels were associated with within-woman changes in facial attractiveness ratings, although these differences were small (Jones et al. 2018b). Another study found that, after controlling for body mass index (BMI), attractiveness ratings of women's bodies were positively correlated with estrogen and testosterone levels, but not progesterone (Grillot et al. 2014). Hence, more research is necessary to clarify which aspects of women's attractiveness vary with which steroid hormones.

Generally, Miller et al. (2007) found that women who were using HCs did not experience an increase in tips mid-cycle. It is possible that the increase in tips that naturally cycling women had around ovulation resulted from subtle changes in their own behavior that influenced the tip amounts they received from patrons, or a combination of their own behavior and physical cues to their fertility status (see Thornhill and Gangestad 2008). Men also perceive their female partners as more attractive during their partner's follicular phase compared to either her luteal phase or when she is using HCs (Cobey et al. 2013a). Furthermore, women using oral contraceptives do not have an increase in vocal attractiveness across their cycle (Ostrander et al. 2018; Pipitone and Gallup Jr 2008). Attractiveness ratings of women's body odor is influenced by HCs such that their body odor is not rated as more attractive at mid cycle (Kuukasjärvi et al. 2004). Although research indicates that women's attractiveness to others may be influenced by HC use, no study to date has considered whether different progestin types, for examples more androgenic versus more progestogenic varieties, differentially impact these associations.

Steroid hormones may also influence women's perceptions of their current romantic relationship (reviewed by Hahn and Cobey 2019; Welling 2013; Welling and Burriss 2019). Women experience an increase in sexual desire around ovulation, but this increase in desire for their partner is moderated by a number of partner-dependent factors (e.g., how attractive or sexually desirable their partner is, Larson et al. 2013; which markers of genetic quality their partner displays, Gangestad et al. 2005).

Fluctuations of progesterone across the cycle have also been positively associated with desire for and commitment to current partners (Jones et al. 2005a; Roney and Simmons 2016) and negatively associated with desire for extra-pair partners (Roney and Simmons, 2016). Sexual satisfaction is related to relationship satisfaction (e.g., Byers 2005; Sprecher 2002), and changes in endogenous progesterone levels may influence how sexually satisfied an individual is with her relationship. Furthermore, other important behaviors related to relationship dynamics may also be influenced by endogenous hormones across the menstrual cycle (e.g., mate retention behaviors of male partners, Gangestad et al. 2002; female jealousy, Cobey et al. 2012), although whether and how progesterone is implicated is unclear.

These aspects of women's relationships have also been shown to be influenced by the use of synthetic hormones. Women taking HCs report more frequent use of mate retention behaviors (i.e., behaviors aimed at monopolizing a partner's time and preventing them from straying from a relationship) compared to women who were natural cycling (Welling et al. 2012). Moreover, the male partners of women taking HCs reported more mate retention behaviors compared to men who were partnered with naturally cycling women. This increase in mate retention behaviors was associated with the amount of synthetic estradiol in participant's HCs, such that women taking HCs with higher doses of estradiol reported higher levels of mate retention behavior. The dose of progestin was not associated with mate retention behaviors, but the authors did not consider different progestin classes. This study is one of few that have considered unique dosage effects of different contraceptive formulations on women's romantic behaviors. Roberts et al. (2012) found that when women who were taking oral contraceptives when they met their current partner scored lower on measures of sexual satisfaction compared to women who were naturally cycling when they met their current partner. Oral contraceptives users were more likely to initiate a separation if it eventually occurred. Other research has found that women who met their husbands while they were taking contraceptives became less satisfied with their partner when they discontinued oral contraceptive use if their husband had a relatively less attractive face, but more satisfied with their partner if they had a relatively attractive face (Russell et al. 2014; see Roberts et al. 2014 for review of congruency hypothesis, although see Jern et al. 2018). Intrasexual competition may also be influenced by HC use, such that partnered women using HCs are less intrasexually competitive than their single counterparts and women who are naturally cycling (Cobey et al. 2013b). Female intrasexual competition has been linked to testosterone (Hahn et al. 2016), so it would follow that women using contraceptives may score lower on intrasexual competition due to the global reduction in androgen production caused by contraceptive use.

Taken together, these results suggest that HCs could influence women's preferences for opposite-sex partners as well as important aspects of their romantic relationships (for review, see Hahn and Cobey, 2019; Welling 2013). The overwhelming majority of these studies, however, have categorized HS users as a single group and compared them to women who were not currently using HCs. Although this approach can capture broad differences between HC users and non-users and some of the effects initiating HCs may have on mate preferences, they cannot capture differences in mate preferences that are due to unique pharmacological properties of different progestin types. The limited existing large-scale research (e.g., Skovlund et al. 2016) indicates that different progestin types contribute to specific psychological and behavioral outcomes.

Accounting for the unique properties of different progestin types may lead to a better understanding of if and how HCs influence mate choice. For instance, if some women are particularly susceptible to mood changes when using HCs due to interactions with the GABAergic system, it is possible that we may also observe differential sensitivity to changes or differences in mate preferences based on various progestin use and individual differences in progestin sensitivity. Yet, with very few exceptions (Cobey et al. 2012; Grøntvedt et al. 2017; Welling et al. 2012), research has failed to consider the effects of different contraceptive dose, progestin formulation, or administrative route.

Discussion

From an evolutionary perspective, progesterone, like other hormones, can be considered important for coordinating system-wide responses to allocate energy and resources to the most fitness-maximizing options given one's current environment or life history (Roney 2016). From this perspective, it is clear that progesterone plays an important part in coordinating interpretation and responses to social cues, such as emotional expression, social rejection, and romantic and sexual stimuli. However, progestins differ from progesterone in a number of important ways at the cellular level (Africander et al. 2011; Louw-du Toit et al. 2017; Schindler 2013) and there is evidence that progestins differentially influence the nervous system and some cognitive mechanisms (reviewed in Giatti et al. 2016; Pletzer and Kerschbaum 2014). It is presently unclear if these differences manifest at the behavioral level. Unlike research investigating the effects of progestins on women's affect and sex drive, which tend to focus on clinical populations, research investigating the influence of HCs on women's mating behavior and psychology have largely ignored the unique qualities of different progestins. Research in this area has typically compared naturally cycling women to women using only oral contraceptives, and oral contraceptive users have been grouped into a single comparison group (e.g., Feinberg et al. 2008; Jones et al. 2005a; Roberts et al. 2012). Details about the type of oral contraceptives women are using are rarely mentioned or accounted for in these studies, nor are other important factors, such as whether women are taking their active pills or inactive pills at the time of survey or if they are using monophasic versus triphasic pill formulations (although see Cobey et al. 2012; Welling et al. 2012). Women using other forms of HCs (i.e., vaginal ring, hormonal IUD, hormone injection, subdermal implant) are either underrepresented in these research paradigms or absent. However, the way progestins are administered has effects on pharmacokinetics (i.e., their bioavailability, distribution, metabolism, and excretion; Kuhl 2005; Stanczyk et al. 2013), which is reflected in their effects on women's affect (Skovlund et al. 2016). It is therefore likely that these idiosyncrasies associated with different progestins and administrative routes may also be reflected in differential effects on women's mating psychology and behaviors.

Understanding the ways that progesterone shapes adaptive responses to social input (for a review, see Gangestad and Grebe 2017) will be important for predicting and studying the ways that synthetic progestins modulate these systems. For instance, if progesterone facilitates perception of social information (e.g., emotional expression; Maner and Miller, 2014) and the desire for social closeness, particularly following social exclusion (e.g., Seidel et al. 2013), then might progestins that more strongly

interact with the progesterone receptor exaggerate these responses? This increase and sustained sensitivity to social information may explain some previously reported relationships in the literature, such as findings that women using HCs and their partners report higher mate retention behaviors than women who are naturally cycling and their partners (e.g., Welling et al. 2012). As reviewed by Welling (2013), hormones that fluctuate across the menstrual cycle may be important for coordinating mate choice decisions as well as satisfaction in subsequent long-term relationships. If endogenous patterns of progesterone production are important for optimizing these decisions from a fitness perspective, then the alteration of these systems via synthetic progestin exposure may have down-stream consequences. Indeed, some research has found that whether women's hormonal contraceptive status remained the same or changed before versus after meeting their romantic partner (i.e., congruent versus incongruent use of HC) predicts their sexual satisfaction with that partner (e.g., Roberts et al. 2014; although see Jern et al. 2018).

A recent study by Grøntvedt et al. (2017) used a novel approach for investigating these differences in progestins and how they may influence women's evolved mating psychology. When investigating the association between hormone dose and the frequency of sexual intercourse, they collected detailed information about the brand and type of contraceptive that participants used and then assigned an absolute progestin and estradiol dose delivered to each participant based on the amount of each compound supplied by their brand of contraceptive. Because it is difficult to compare progestins on a continuous spectrum due to their unique biological qualities (e.g., bioavailability, affinity for the progesterone receptor, androgenic effects), the authors placed the progestins represented in their sample on a single scale adjusted for potency by using the daily dose necessary for ovulation suppression. They also accounted for the known androgenicity and route of administration of each progestin. Their results indicated that as estradiol levels decreased and progestin levels increased, women's reported faithfulness to their partner became more predictive of reported sexual intercourse frequency. This is an instructive example of how behavioral researchers interested in the effects of contraceptives on women's mating psychology can more accurately capture unique qualities of progestins, and this type of approach is a necessary step toward clarifying a field of study that has produced some conflicting or ambiguous results (see, e.g., Jones et al. 2005a, 2005b, 2018b, 2018c).

Progesterone has specific biological and psychological effects, some of which have only recently been elucidated (i.e., non-genomic effects of progesterone and its role as a neurosteroid; Baulieu 1997; Thomas 2008). Synthetic progestins have been developed to mimic the activity of progesterone at the PR, and, more recently, to mimic some of the anti-mineralocorticoid effects of progesterone. However, progestins may influence many non-reproductive capacities in women due to their unique pharmacokinetics, interactions with off-target steroid receptors, effects on endogenous steroid hormone synthesis, different bioactive metabolites, and their dosage and route of administration (See Table 2 for important dimensions along which HCs vary and suggestions on ways researchers can account for these differences). Future research investigating the effects of these compounds on women's mood, affect, sex drive, and mating preferences and romantic relationships, as well as other aspects of behaviors, should account for these differences in progestins when possible. Moreover, previous research should be replicated while accounting for these differences. Accounting for individual differences in

Table 2 Unique aspects of hormonal contraceptives and suggestions for how researchers may investigate the potential effects these differences have on variables of interest

Dimension of concern	Variability between hormonal contraceptives	Methodological consideration
Effective dosage of progestin	All contraceptives deliver enough progestin to alter ovulation and/or alter uterine environment to reduce likelihood of fertilization. However, some contraceptive pills deliver relatively more progestin than is required for ovulation prevention compared to others (e.g., mini-pills or micro-mini progestin-only pills).	Standardizing effective progestin dosage across contraceptive types (e.g., Grøntvedt et al. 2017) and controlling for differences in effective dosage may reveal dosage-specific effects. Comparing women across multiple weeks of a tri-phasic or bi-phasic combined oral contraceptive regimen may reveal within-women dosage effects of synthetic hormones.
Activity of progestin at other steroid receptors	Some progestins have demonstrated marked androgenic activity (e.g., levonorgestrel and medroxyprogesterone acetate). Particularly, first and second generation progestins are more androgenic than fourth generation progestins like drospirenone and dienogest. Progestins also vary in their activity at the mineralocorticoid and glucocorticoid receptor activity (see Table 1).	Grouping progestins by strength of activity at various receptors (e.g., AR, ER, GR, MR) or controlling for differences in activity at these receptor sites may reveal progestin-specific effects and implicate other steroid hormone systems in the behavior of interest.
Estradiol/Progestin ratio	Hormonal contraceptives vary in their delivery of estradiol and the relative ratio of estradiol to progesterone.	Researchers can calculate the effective dosage of progestin contained per contraceptive brand/type and then calculate the relative estradiol to effective progestin dosage to include in analyses including women using hormonal contraceptives.
Time since administration	Pharmacokinetic profiles for hormonal contraceptives vary based on administrative route. Oral contraceptives cause roughly daily fluctuations in plasma hormone levels that depend on when pills are taken and when women are using active versus inactive pills. Longer-acting forms of contraceptives (e.g., injections, implant, IUDs) also result in varying levels of plasma hormone concentration, albeit over longer time-spans	Researchers could consider comparing women using active versus inactive (placebo) oral contraceptive pills. Methods assessing women using oral contraceptives may control for time since they consumed their most recent pill, or assess individuals before and after taking their oral contraceptives (e.g., at times when plasma levels should be lowest and highest). For longer-acting methods, researchers could compare women who just received their treatment (e.g., an injection) and women who are almost due for a new treatment.
Route of administration	There are substantial pharmacokinetic differences between oral contraceptive pills (i.e., enteral administrative route) and vaginal rings, IUDs, implants, and skin patches (i.e., parenteral administrative route).	Administrative route is associated with differences in important health outcomes (e.g., depression; Skovlund et al. 2016). Researcher could intentionally recruit women using non-oral forms of hormonal contraceptives and compare responses based on enteral versus parenteral administrative routes

Table 2 (continued)

Dimension of concern	Variability between hormonal contraceptives	Methodological consideration
		broadly, or by specifically comparing each administrative route present in their study (e.g., compare IUD users to implant users and injection users). Researchers should also intentionally recruit women using non-oral routes of hormonal contraceptives because these groups are largely under-represented in psychobehavioral research on hormonal contraceptives.

sensitivity to endogenous and exogenous hormones will also be a key aspect of research clarifying the effects of progestins on these domains. Factors such as a history of PMDD and depression, and individual genetic differences, such as androgen receptor polymorphisms or mineralocorticoid receptor haplotype, may moderate the effects that women experience when they initiate HC use (Elaut et al. 2012; Hamstra et al. 2017; Joffe et al. 2003).

Future behavioral research accounting for these unique differences in progestin compounds may be influential and informative for the development of new contraceptive progestins and hormonal replacement therapies. This line of research may also be instructive for the development of male HCs and hormonal transition therapies (e.g., menopausal hormone replacement therapy). HCs have been important for women's ability to take control of their fertility and reproductive choices, and the use of HCs has led to improved economic and health outcomes for women and their children (Bailey 2006; Goldin and Katz 2002), and thus potential side effects should be weighed against these benefits. Nevertheless, a complete understanding of the effects that different synthetic progestins have on users' physiology, psychology, and behavior is essential for providing both practitioners and the individuals using these drugs with the information necessary to make informed medical decisions. Currently, research accounting for these differences is lacking.

Compliance with ethical standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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