



Progesterone – Friend or foe?

Inger Sundström-Poromaa^{a,*}, Erika Comasco^b, Rachael Sumner^c, Eileen Luders^{d,e}

^a Department of Women's and Children's Health, Uppsala University, Sweden

^b Department of Neuroscience, Science for Life Laboratory, Uppsala University, Uppsala, Sweden

^c School of Pharmacy, University of Auckland, New Zealand

^d School of Psychology, University of Auckland, New Zealand

^e Laboratory of Neuro Imaging, School of Medicine, University of Southern California, Los Angeles, USA



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ABSTRACT

Estradiol is the “prototypic” sex hormone of women. Yet, women have another sex hormone, which is often disregarded: Progesterone. The goal of this article is to provide a comprehensive review on progesterone, and its metabolite allopregnanolone, emphasizing three key areas: biological properties, main functions, and effects on mood in women. Recent years of intensive research on progesterone and allopregnanolone have paved the way for new treatment of postpartum depression. However, treatment for premenstrual syndrome and premenstrual dysphoric disorder as well as contraception that women can use without risking mental health problems are still needed. As far as progesterone is concerned, we might be dealing with a two-edged sword: while its metabolite allopregnanolone has been proven useful for treatment of PPD, it may trigger negative symptoms in women with PMS and PMDD. Overall, our current knowledge on the beneficial and harmful effects of progesterone is limited and further research is imperative.

Introduction

Estradiol is commonly understood as the “prototypic” sex hormone of women. Estradiol modulates mood and cognition (Sherwin, 2012; Comasco et al., 2014) and estradiol is strongly associated with all important reproductive shifts throughout the fertile life of a woman, ranging from puberty and the onset of the menstrual cycle, pregnancy and the postpartum period, as well as perimenopause and eventually menopause. Yet, women have another sex hormone, which is often disregarded: Progesterone. The goal of this article is to provide a comprehensive review on progesterone putting emphasis on three key areas: biological properties (Section 1), main functions (Section 2), and effects on mood (Section 3),¹ as summarized in Fig. 1. As many women suffer from negative side effects of progesterone in the emotional realm, the final section on mood is the most detailed and extensive. In that section, we aimed to create a comprehensive synthesis of the evidence on the role of progesterone in relation to women's mental health. For this purpose, we did not only consider several angles but also opted for presenting controversial findings.

1. Biological properties

1.1. Synthesis

In women, progesterone is mainly produced by the corpus luteum in the ovaries. The corpus luteum develops from the remnants of the ovulating (dominant) follicle, under the influence of luteinizing hormone (LH); it is a highly vascularized organ that exists for about 14 days each menstrual cycle (Speroff and Fritz, 2010). In contrast to the relatively complicated synthesis of estradiol – requiring several enzymatic steps and also involving two different cell types (the theca cells and the granulosa cells of the growing follicle) – the synthesis of progesterone is relatively simple (Stocco, 2001): Progesterone can be synthesized by most cells in the corpus luteum and is produced by two enzymatic steps: first by conversion of cholesterol to pregnenolone in the mitochondria (via the cholesterol side-chain cleavage enzyme, also known as P450_{scc}), and then by conversion from pregnenolone to progesterone (via the enzyme 3 β -hydroxysteroid dehydrogenase), as illustrated in Fig. 2. In addition to the ovaries, progesterone can also be produced in the adrenals, in the placenta, and in the brain.

* Corresponding author at: Department of Women's and Children's Health, Uppsala University, 751 85 Uppsala, Sweden.

E-mail address: inger.sundstrom@kbh.uu.se (I. Sundström-Poromaa).

¹ For a complementary review on links between progesterone, premenstrual dysphoric disorder and brain structure and function, please refer to a companion paper in this special issue (Dubol et al., 2020).

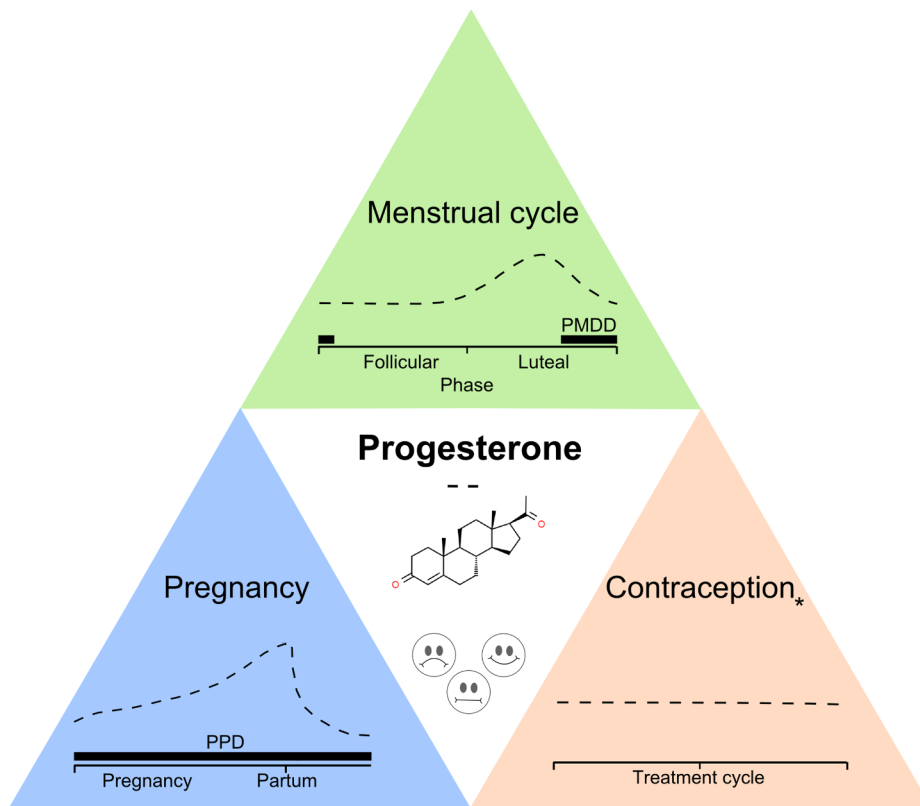


Fig. 1. The goal of this article is to provide a comprehensive review on the female sex hormone progesterone. As many women suffer from negative side effects of progesterone, the final section on mood is the most detailed, focusing on the menstrual cycle and premenstrual dysphoric disorder, pregnancy and hormonal contraceptives. The figure displays roughly how progesterone levels fluctuate during these conditions and treatments.*The hormonal IUD does not suppress fluctuations in progesterone.

1.2. Metabolism

Progesterone is metabolized primarily in the liver by the enzymes 5 α -reductase and 3 α -hydroxysteroid oxidoreductase, resulting in a number of metabolites, among them allopregnanolone (3 α -hydroxy-5 α -pregnan-20-one) and pregnanolone (3 α -hydroxy-5 β -pregnan-20-one), as shown in Fig. 2. The enzymes needed for progesterone metabolism are present in the corpus luteum and in the brain (Ottander et al., 2005; Pluchino et al., 2019). A functionally relevant amount of allopregnanolone can be synthesized in the brain (Puia et al., 2003; Purdy et al., 1991), but when progesterone levels are high (i.e., during the luteal phase of the menstrual cycle and during pregnancy), most of the allopregnanolone found in the brain is likely synthesized in the periphery (Ottander et al., 2005). During stress, the adrenal glands also synthesize allopregnanolone, and the adrenal production accounts for a large extent of the stress-induced peripheral and brain levels of allopregnanolone (Genazzani et al., 1998; Purdy et al., 1991). Local production of allopregnanolone in the brain is also noted during stress (Purdy et al., 1991).

1.3. Fluctuations

In women, progesterone is essentially only present during the luteal phase of the menstrual cycle and during pregnancy. Notably, during that time, progesterone serum concentrations are approximately 100-fold greater than estradiol serum concentrations. That is, estradiol serum concentrations exist in the pico-molar range, whereas progesterone serum concentrations are found in the nano-molar range. Since progesterone synthesis is stimulated by pulsatile LH release, it displays a pulsatile release pattern with considerable variability across each pulse within each woman (Filicori et al., 1984). Moreover, there is also considerable variability in progesterone levels across women, the reason why it is hard to establish thresholds for what determines a progesterone deficiency (Mesen and Young, 2015). Neither progesterone nor any of its metabolites display a diurnal pattern (Segebladh

et al., 2013). During the mid-luteal phase, progesterone levels above 25 nmol/l indicate successful ovulation, but progesterone levels in the range of 40–60 nmol/l may exist. Progesterone levels as they occur over the menstrual cycle are provided in Table 1. Stress during the follicular phase may lead to slightly elevated progesterone levels, in the range of 5 nmol/l (Genazzani et al., 1998). If, on the other hand, higher progesterone levels are encountered in the luteal phase, it is usually a sign of successful implantation and pregnancy (for detailed changes during pregnancy, see Section 2.1).

Serum concentrations of allopregnanolone temporally follow those of progesterone with an off-set of 2–3 days, and the difference between menstrual cycle phases is less pronounced (see Table 1). That is, allopregnanolone levels increase from 1 nmol/l in the follicular phase to approximately 2 nmol/l in the luteal phase (Wang et al., 1996), and secretion is pulsatile (Genazzani et al., 2002). Of note, independent of ovulation and pregnancy, acute stress is accompanied by rising levels of allopregnanolone as shown in rats (Sze et al., 2018; Barbaccia et al., 1998, 1996; Purdy et al., 1991), whereas chronic stress has the opposite effect and lowers allopregnanolone levels (Locci and Pinna, 2017). In humans, acute stress doubles the normal allopregnanolone levels (Genazzani et al., 1998), whereas chronic stress has more subtle effects (Droogleever Fortuyn et al., 2004).

1.4. Progesterone in the brain

Being a steroid hormone, progesterone is highly lipophilic and easily passes through the blood-brain barrier. Progesterone is accumulated in the brain, so that progesterone concentrations in some areas of the brain are actually higher than measured in the serum of the blood, as assessed in female rats (Bixo et al., 1986). In women, the brain region with the highest concentration of progesterone seems to be the amygdala, followed by the cerebellum, the nucleus accumbens and the hypothalamus (Bixo et al., 1997). Similar to progesterone, allopregnanolone and other progesterone metabolites are also accumulated in the brain. In women, the highest concentrations of allopregnanolone are

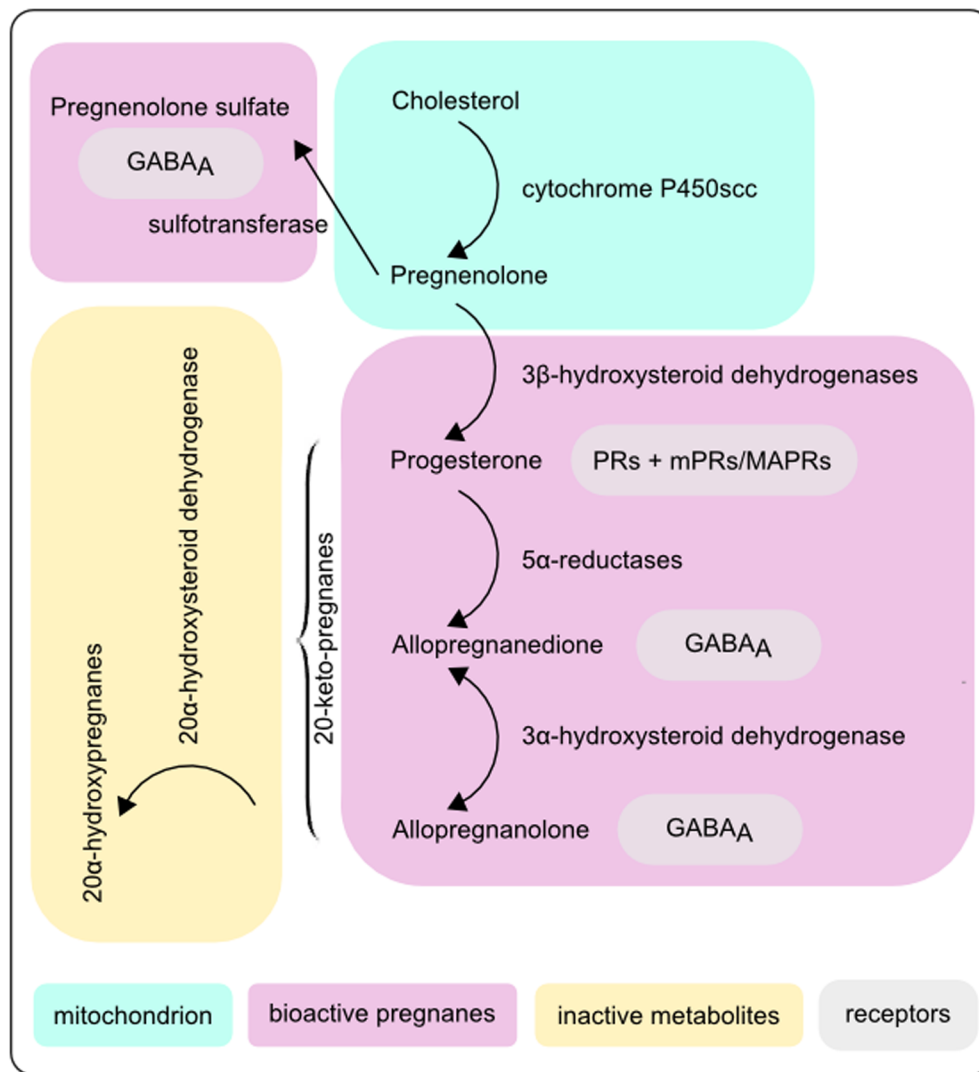


Fig. 2. A schematic representation of the progesterone synthesis, metabolism route, as well as the interaction with progesterone receptors. Pregnenolone is synthesized from cholesterol by cytochrome P450scc, and then converted to progesterone by the 3 β -hydroxysteroid dehydrogenase. Progesterone is metabolized to allopregnanedione by the 5 α -reductases, further converted to allopregnanolone by the 3 α -hydroxysteroid dehydrogenase. Progesterone exerts its action by binding to intracellular receptors (PRs) to regulate gene transcription, by interacting with membrane receptors (mPRs) and membrane-associated kinases (MAPRs) in extranuclear compartments. Allopregnanolone and other progesterone metabolites act as positive modulators on the GABA_A receptors. The enzyme 20 α -hydroxysteroid dehydrogenase catalyzes the conversion of the GABA-active progesterone metabolites into inactive metabolites. Additionally, pregnenolone is converted into pregnenolone sulfate by sulfotransferase. The metabolic pathways involving the conversion of progesterone to androgens, estrogens and corticosteroids are not mentioned in the present review.

found in the basal hypothalamus, followed by the substantia nigra and the amygdala (Bixo et al., 1997; Corpechot et al., 1997).

1.4.1. Progesterone receptors

The progesterone receptors (PR), PR-A and PR-B, which are both transcribed from a single gene, are not only highly expressed in brain areas associated with reproduction, but also in areas of importance for cognitive function and emotional processing,² as derived from animal research (Brinton et al., 2008; Gruber et al., 2002; Schumacher et al., 2014). More specifically, while PRs have not yet been mapped in the human brain, animal data suggest that PRs are distributed throughout the hypothalamus, amygdala, hippocampus, thalamus and the frontal cortex (Holder et al., 2015; Guerra-Araiza et al., 2000, 2003).³ Interestingly, PRs are strongly induced by estradiol within the hypothalamus, whereas the dependency on estradiol for PR expression is only modest or weak in other regions, as demonstrated in the rat brain (MacLusky and McEwen, 1978). The down- or up-regulation due to progesterone treatment only affects those PRs that are inducible by

² Outside the brain, PR-A and PR-B have strikingly different actions, where PR-B seems necessary for normal mammary gland development, while PR-A is required for uterine functions (Schumacher et al., 2014).

³ Similar to estradiol receptors, which are expressed in human brains within the cerebral cortex as well as in subcortical regions, such as the hypothalamus, amygdala, hippocampus, and claustrum (Osterlund et al., 2000a, 2000b).

estradiol. In other words, in rats, PRs that are not regulated by estradiol are also not inhibited by progesterone; they continue to be expressed – albeit are not necessary functional – even with prolonged progesterone treatment (Schumacher et al., 2014). Moreover, in rats, the location of PR in the hypothalamus appears to be primarily nuclear, while in other areas of the brain PRs are found at axons, dendrites and even synapses (Schumacher et al., 2014).

In addition to mechanisms pertaining to PR-A and PR-B, progesterone can exert its effects via membrane receptors. Two families of membrane receptors have been described: 1) the progestin and AdipoQ receptor (PAQR) family, which includes five membrane progesterone receptors (mPR), specifically mPR α , mPR β , mPR γ , mPR δ , and mPR ϵ ; and 2) the membrane-associated progesterone receptor (MAPR) family, which includes neudesin, neuferricin, and two progesterone receptor membrane components (PGRMC), specifically PGRMC1 and PGRMC2 (Hasegawa et al., 2016). Most of these receptors have been described in relation to the reproductive organs, but mPR β , neudesin, and PGRMC1 are expressed in the rodent brain and appear to influence neurogenesis (Kasubuchi et al., 2017; Petersen et al., 2013; Novais et al., 2018). Of note, peripheral PGRMC1 levels do not vary throughout the menstrual cycle, but are down-regulated in menopausal women or in women suffering from premature ovarian insufficiency (Schuster et al., 2010).

1.4.2. Other mechanisms

Yet another route by which progesterone may influence emotional

Table 1
Progesterone and allopregnanolone serum concentrations across a 28-day standardized menstrual cycle.

Menstrual cycle day	Progesterone (nmol/l)		Allopregnanolone (nmol/l)	
	mean	SD	mean	SD
1	4.49	3.36	0.87	0.36
2	3.00	1.70	0.73	0.29
3	2.18	0.78	0.79	0.34
4	2.23	0.86	0.77	0.23
5	2.55	2.11	0.51	0.16
6	2.42	0.99	0.47	0.18
7	2.41	0.94	0.48	0.04
8	2.06	0.88	0.47	0.12
9	1.92	0.82	0.47	0.16
10	2.04	1.09	0.44	0.13
11	2.29	1.19	0.44	0.20
12	2.19	0.97	0.81	0.44
13	2.62	1.21	0.69	0.37
14	4.15	1.56	0.88	0.30
15	5.22	1.91	1.02	0.35
16	12.33	5.33	1.30	0.73
17	21.03	7.04	1.44	0.45
18	30.31	11.75	1.64	0.49
19	34.55	12.27	1.80	0.66
20	41.68	16.43	1.83	0.69
21	42.95	17.64	1.87	0.68
22	40.82	15.74	1.96	0.64
23	41.79	17.47	1.96	0.71
24	36.10	15.88	1.87	0.68
25	27.06	12.48	1.68	0.71
26	21.17	12.47	1.39	0.62
27	13.59	7.48	1.14	0.46
28	7.25	5.35	1.12	0.49

Blood samples of 32 menstrual cycles from a group of 20 women with and without premenstrual syndrome (Wang et al., 1996). For the reference cycle, women provided daily blood samples for progesterone and allopregnanolone assays on cycle days 1–4, and from cycle day 10 throughout the remaining cycle, and further until the 4th day of menstrual bleeding. Between cycle days 4 and 10, occasional blood samples were taken. The average age of the women was 36.6 years (range 25–44 years). All cycles in the reference group were ovulatory, as defined by plasma progesterone values exceeding 15 nmol/l.

and behavioral circuits in the brain is via its metabolism to GABA-ergic neurosteroids (see Fig. 2). Both allopregnanolone and pregnanolone act as positive allosteric modulators on the γ -amino-butyric acid receptor A (GABA-R). GABA-Rs are distributed widely throughout the human central nervous system, and can be found within the amygdala, hippocampus and hypothalamus (Stefanits et al., 2018; Waldvogel et al., 2017). In fact, GABA neurotransmission is the most widespread inhibitory system in the brain. Thus, progesterone exerts a major impact on the brain via its metabolites. By binding to the GABA-R, allopregnanolone has sedative, anxiolytic, anti-convulsant, neuroprotective properties and memory-impairing effects, both in rodents and humans (Brunton, 2015; Melcangi et al., 2011; Kask et al., 2008a). Interestingly, as shown in rats (Zhu et al., 2001), the different progesterone metabolites seem to have different pharmacodynamics properties (e.g., allopregnanolone is more potent than pregnanolone to induce sedation).

Adding further complexity to the picture, studies on primates, rodents and to a certain extent humans, demonstrate that progesterone and also allopregnanolone act as modulators for other neurotransmitter systems, such as the serotonergic, cholinergic, and dopaminergic systems (Comasco et al., 2014; Barth et al., 2015). Most studied is the serotonergic neural system that projects to nearly every area of the forebrain with substantial input to the hippocampus, amygdala and prefrontal cortex (i.e., areas with rich abundance of PRs). Animal studies have indicated widespread interactions between progesterone (and estradiol) and the serotonin neurotransmitter system (Betha et al., 2009). In fact, the up- or down-regulation of enzymes that affect

monoaminergic neurotransmission has been associated with progesterone. For example, progesterone down-regulates monoamine oxidase A (MAOA) mRNA levels in the dorsal raphe nucleus and hypothalamic nuclei of macaque monkeys (Gundlah et al., 2002), but up-regulates MAO-A activity in hypothalamic areas of rats (Luine and Rhodes, 1983).

In humans, the relationship with these neurotransmitters has been primarily examined for estradiol; fewer studies have considered the combined effect of estradiol and progesterone (Hall and Steiner, 2013; Henderson and Greicius, 2010). In healthy women, there seems to be a link between lower serum allopregnanolone levels in the follicular phase and higher serotonin receptor transporter binding in the prefrontal cortex (Sundstrom Poromaa et al., 2018). Furthermore, there is an increased availability of serotonin receptors 1A (5HT_{1A}) in the raphe nuclei during the luteal compared to the follicular phase (Jovanovic et al., 2006). Moreover, there seem to be complex and not yet well defined interactions between allopregnanolone and the glutamatergic and dopaminergic transmitter systems, which are potentially relevant for neurological and psychiatric disorders (Bali and Jaggi, 2014).

2. Main functions

2.1. Preparing for and maintaining pregnancy

Progesterone has crucial functions in preparing the uterus for a pregnancy as well as in maintaining pregnancy. More specifically, progesterone prepares the endometrium for implantation. The progesterone peak, occurring 8 days after the preovulatory LH peak, coincides with the 2-day endometrial implantation window, when a blastocyst can attach to the endometrial surface (Nikas and Makrigiannakis, 2003). Once pregnancy is established, progesterone is essential for immunotolerance, and later for inhibition of myometrial contractility and maintained cervical integrity (Conde-Agudelo et al., 2018). Moreover, progesterone functions as vasodilator (Rylance et al., 1985; Ngene and Moodley, 2019), thus contributing to reducing blood pressure during pregnancy. On that note, pregnant women with preeclampsia have lower levels of progesterone, and treatment of gestational hypertension with a progesterone synthetic metabolite has been proven efficacious (Amaral et al., 2014). This protective effect of progesterone on the vascular level decreases towards term (Ngene and Moodley, 2019). Allopregnanolone, in turn, has important neuroprotective effects in the developing fetal brain (Hirst et al., 2014). Clinically, vaginal progesterone treatment is used to prevent preterm birth in women with shortened cervix (Conde-Agudelo et al., 2018) as well as for the support of the corpus luteum during *in vitro* fertilization cycles (Barbosa et al., 2018).

In early pregnancy, the corpus luteum continues to secrete progesterone, but from the 7-9th week of pregnancy, the placenta gradually takes over endocrine functions together with the developing fetal endocrine system. Known as the “feto-placental unit”, this system releases increasing amounts of hormones into the maternal bloodstream. Consequently, the level of numerous hormones (progesterone, estrogens [estradiol and estrone], lactogen [known as prolactin in non-pregnant women], testosterone, corticotrophin-releasing hormone [CRH], and cortisol) all rise continuously through the 40th week of pregnancy, followed by a drastic drop in hormone levels after childbirth (Dorr et al., 1989; Stalla et al., 1989; Jung et al., 2011; Harris et al., 1994). Before childbirth, progesterone reaches levels of 200–2000 nmol/l (Dorr et al., 1989) and allopregnanolone rise by tenfold (Pennell et al., 2015; Dombroski et al., 1997; Parizek et al., 2005).

In humans, the start of labour seems to depend on a functional progesterone withdrawal, via altered binding or expression of PRs (Zakar and Hertelendy, 2007), rather than a reduction in progesterone per se. So, while in humans and other primates progesterone levels remain high until after delivery, in non-primate mammals, a sudden drop in progesterone precedes parturition. Following birth, there is a

rapid and dramatic reduction in progesterone and allopregnanolone levels. In fact, half of progesterone is eliminated from the circulation in 38 min, and luteal phase levels (or just above) are reached at about 2–3 h after childbirth (Lofgren and Backstrom, 1990). Allopregnanolone levels are reduced within approximately half an hour after birth and return to non-pregnant levels five days after childbirth (Hill et al., 2001).

In non-human mammals, the complex endocrine changes across pregnancy and the postpartum period prepare the dams for maternal attachment and behaviour, and this appears, at least partly, to be the case in humans as well (Bridges et al., 1985, 1978; Feldman et al., 2007; Fleming et al., 1989, 1997a, 1997b; Lonstein et al., 2015; MacKinnon et al., 2014; Pedersen, 1997; Siegel and Rosenblatt, 1978). As demonstrated in rodents, key regions in reproductive physiology (such as the medial preoptic area), and motivational circuits (such as the ventral tegmental area) undergo remodelling throughout the pregnancy in preparation for motherhood (Keller et al., 2019). Human studies also suggest major structural brain changes after birth (Oatridge et al., 2002; Kim et al., 2010; Hoekzema et al., 2017; Luders et al., 2018, 2020; Lisofsky et al., 2019), although the role of progesterone for these changes is yet to be determined.

Owing to its effect on the GABA-R, the fatigue experienced by many women during the first trimester has been proposed to be an effect of allopregnanolone (Turkmen et al., 2011). When intravenously administered to non-pregnant women, similar allopregnanolone serum concentrations have sedative effects (Timby et al., 2006) and impair memory (Kask et al., 2008a). Women in later stages of pregnancy are usually not affected by these symptoms, so a tolerance seems to develop during pregnancy (Turkmen et al., 2011). Notably, the increase in progesterone and allopregnanolone during pregnancy is accompanied by a decreased GABA content in the brain tissue as well as altered gene expression and function of GABA receptors, such as an increased tonic inhibition in the hippocampus in animals (Licheri et al., 2015; Smolen et al., 1987, 1993; Glaser et al., 1992), and altered peripheral expression of GABA-R subtypes in humans (Bhandage et al., 2015). Similarly, the cerebrospinal fluid (CSF) in women undergoing elective caesarean section shows significantly lower levels of GABA than the CSF in non-pregnant women (Altemus et al., 2004).

2.2. Hormonal contraception

Synthetic progesterone, also called progestogens or progestins, is used for hormonal contraception (HC). Progestogens may be derived from testosterone or progesterone. Effectively, progestogens inhibit ovulation – either on their own as progestogen-only pills, progestogen implants or progestogen injections, or in combination with estradiol (or synthetic estrogens) as combined hormonal contraception (CHC). Progestogens bind to a range of steroid hormone receptors (e.g., progesterone, testosterone, mineralocorticoid, and glucocorticoid receptors), and also exert agonist or antagonist actions at these receptors. Given the differential binding to these receptors, progestogens have different efficacies and side effects (Endrikat et al., 2011). Roughly, progestogens are sub-grouped as those with androgenic properties (e.g., levonorgestrel [LNG]), and those with anti-androgenic properties (e.g., drospirenone or cyproterone acetate), based on their agonist or antagonist actions at the testosterone receptor and their ability to increase sex-hormone binding globulin levels; the latter affects the bioavailable testosterone levels in women (Odland et al., 2002). In addition, progestogens are grouped according to dose and their influence on follicular growth in the ovary (i.e., their effect on endogenous estradiol concentrations): Medium-dosed preparations (e.g., implants and desogestrel-containing pills) maintain estradiol concentrations at 200–300 pmol/l (Croxatto and Makarainen, 1998), while high-dose preparations (e.g., injections) lead to a suppression of estradiol synthesis altogether (Mishell, 1996).

2.3. Other uses

Combined estradiol and progestogen treatment is also prescribed as menopausal hormone therapy (MHT) to women going through the menopausal transition. For a review on the effects of MHT on neurochemistry and neural correlates of cognition and mood, please refer to Comasco et al. (2014). Interestingly, progesterone, together with estrogen, is nowadays also part of the cross-sex hormone therapy for male-to-female patients with gender dysphoria (Spack, 2013; Prior, 2019). For the effect of this treatment on the brain, please see the neuroimaging studies performed by Lanzenberger and colleagues (Kranz et al., 2014, 2015, 2017; Spies et al., 2016; Seiger et al., 2016).

3. Effects on mood

Progesterone, or allopregnanolone, influence emotion processing and are likely causal factors for the mood symptoms experienced by women with premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). Synthetic progestogens play a role for the mental side effects that have been noted by some hormonal contraceptive users (Lundin et al., 2017; Gingnell et al., 2013) as well as for the minor mood disturbances that have been experienced by postmenopausal women on estradiol and progestogen MHT (Andreen et al., 2006; Gulino et al., 2002; Backstrom et al., 2015). In contrast, continuous exposure to high progesterone, such as during pregnancy, has not been associated with depressed mood, and evidence suggest that allopregnanolone may have protective and mood stabilizing effects during pregnancy and the postpartum period (Hellgren et al., 2014; Kanes et al., 2017; Osborne et al., 2017).

Furthermore, mood effects of progesterone or allopregnanolone must be understood in the context of inter-individual sensitivity, temporal relationships, and serum concentration (or dose). In addition, underlying mental health problems may add to the picture. Many women with major depression report premenstrual worsening (Kornstein et al., 2005) and women with borderline personality disorder display reactive aggression, anger and irritability during the luteal phase (Peters et al., 2020; Eisenlohr-Moul et al., 2018). On top of that, age, parity, environmental influences (e.g., childhood maltreatment and stress), and genetic risk may all shape the individual sensitivity to progesterone (Girdler et al., 2007).

Last but not least, in the presence of stress, progesterone or pregnenolone can be converted into cortisol. Cortisol participates in the stress response and altered levels have been associated with impaired emotion processing as well as mood disorders, including PMDD and PPD (Iliadis et al., 2017, 2015, 2016). On the other hand, allopregnanolone is suggested as potential treatment of stress-related disorders as its level is lowered in the presence of protracted stress, at least in animal models (Locci and Pinna, 2017). For further details on the effect of allopregnanolone in PPD, see Section 4.3.2.2.

3.1. Progesterone and emotion processing

In healthy women, progesterone influences emotion processing, especially emotion recognition accuracy and emotional memories, both at the behavioral level (Sundstrom-Poromaa, 2018) and in the brain (Rehbein et al., 2020; Toffoletto et al., 2014). For a complementary review on links between progesterone, menstrual cycle and brain structure and function, please refer to a companion paper in this special issue (Dubol et al., this issue).

Emotion processing involves the detection and evaluation of salient stimuli; it includes components of attention, emotional arousal, and regulation of arousal. Emotion recognition accuracy appears poorer in the progesterone-dominated luteal phase, or after acute progesterone administration (van Wingen et al., 2007), and this finding seems most relevant for negative emotional stimuli (Guapo et al., 2009; Derntl et al., 2013, 2008a, 2008b). Furthermore, healthy women demonstrate

a negative bias in emotion recognition (Conway et al., 2007); they also respond faster to negative stimuli when progesterone levels are elevated (Derntl et al., 2013; Gasbarri et al., 2008; Masataka and Shibasaki, 2012; Kamboj et al., 2015). In healthy women, this phenomenon has been described as an adaptive heightened sensitivity to physical threat, as raised progesterone levels are thought to prepare the body for pregnancy (Conway et al., 2007).

Emotional memory depends on hypothalamus-pituitary-adrenal (HPA) axis hormones, sympathetic activity and progesterone; it involves the amygdala, hippocampus and prefrontal cortex (Ney et al., 2019). Overall, the literature on progesterone and emotional memory is complicated by varying study designs and methods of measuring memory; it points to domain-specific, rather than generalized effects. For example, a within-subject study reported decreased recognition for negative items in the luteal compared to the follicular phase (Bayer et al., 2014). However, between-subject studies did not detect any difference across cycle phases (Felmington et al., 2012; Maki et al., 2015; Ertman et al., 2011). There are reports of enhanced free-recall but not of an enhanced recognition memory for emotional items in the luteal phase (Ertman et al., 2011). Nevertheless, emotional free-recall and recognition memory were positively correlated with progesterone levels sampled at the time of encoding (Ertman et al., 2011). In addition, memory seems to be enhanced for peripheral details of emotional stories compared to neutral stories in the luteal compared to the follicular phase (Nielsen et al., 2013). Interestingly, re-experiencing in post-traumatic stress disorder is more common following traumatic exposure during the luteal phase (Garcia et al., 2018).

One issue with comparing and interpreting both the positive and negative findings in healthy women is that some of the study outcomes may be driven by the inclusion of women with PMS or sub-threshold PMDD; only very few studies controlled for these disorders (Wittchen et al., 2002; Sveindottir and Backstrom, 2000). The impact of even sub-clinical pre-menstrual symptoms is exemplified in a recent study on startle modulation during the menstrual cycle (Armbruster et al., 2018).

3.2. Premenstrual dysphoric disorder

Among women of childbearing ages, 18% experience at least one mood symptom in the luteal phase, (Wittchen et al., 2002), 2–10% are afflicted by severe premenstrual symptoms, and 2–5% fulfil criteria for PMDD (O'Brien et al., 2011). PMS is often conceptualized as a milder version of PMDD, as fewer symptoms are required for diagnosis. Given the better diagnostic stringency in studies on PMDD, we will focus on PMDD rather than PMS in this review.

PMDD is categorized as a mood disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and is defined by the onset of functionally impairing or distressing affective, behavioral and physical symptoms in the late luteal phase of ovulatory menstrual cycles. The most common symptoms are depression, irritability, mood lability, and anxiety (Epperson et al., 2012; Yonkers et al., 2008). Notably, the severity of symptoms in the luteal phase is in the range of women with moderate or severe depression, and reports of luteal phase suicidal thoughts are not uncommon (Pilver et al., 2013). Because of the severity of symptoms, and the great number of symptomatic days throughout the childbearing period, the disease burden associated with PMDD is estimated to exceed the one associated with major depression (Halbreich et al., 2003).

Women with PMDD demonstrate impaired emotion processing in the luteal phase (Rubinow et al., 2007; Petersen et al., 2016) as well as signs of increased arousal (Epperson et al., 2007), increased emotion-modulated startle response (Bannbers et al., 2011), and reduced sensorimotor gating (Kask et al., 2008b). These findings are corroborated by functional neuroimaging studies, where the neural correlates of PMDD include impaired prefrontal cortex top-down control of emotions that are generated in the limbic system (Comasco and Sundstrom-Poromaa, 2015; Dubol et al., 2020). While these findings are consistent

with the functional neuroanatomy of a range of anxiety disorders (Etkin and Wager, 2007), it is unclear if they manifest as an underlying trait of women with PMDD (i.e., if they are also present in the asymptomatic follicular phase, or if they are specifically triggered by the progesterone increase of the luteal phase).

3.2.1. PMDD and progesterone

Converging evidence suggests that progesterone fluctuations are a key factor for causing PMDD. Research in support of this include the temporal relationship with progesterone levels, findings of symptom relief during gonadotropin releasing hormone (GnRH) agonist-induced anovulatory cycles (Wyatt et al., 2004), the reinstatement of symptoms during GnRH agonist treatment when add-back progesterone is administered (Segebladh et al., 2009a), and the fact that progesterone treatment does not improve the mental symptoms (Wyatt et al., 2001). Additionally, progesterone-induced mood symptoms have been demonstrated in postmenopausal women on MHT (Andreen et al., 2003, 2005, 2006).

Notably, women with PMDD have similar progesterone and allopregnanolone serum concentrations as healthy women (Bixo et al., 2017). This has led to the assumption that women with PMDD have an increased sensitivity to the fluctuations in progesterone levels. Some evidence of increased sensitivity to progesterone is available as progesterone administration, resulting in luteal-phase range serum concentrations, increases amygdala reactivity in healthy women (van Wingen et al., 2008). A similar response has been noted in women with PMDD, but at much lower progesterone concentrations than was needed to elicit an amygdala response in healthy women (Gingnell et al., 2012).

3.2.1.1. Fluctuation, timing and dose of progesterone in relation to PMDD. The acute variation in progesterone (and estradiol) seems to be a key contributor to the PMDD symptoms, as shown in a recent study (Schmidt et al., 2017) administering three months of continuous progesterone and estradiol add-back to women with PMDD on GnRH agonist treatment. In that study it was observed that PMDD symptoms were worse during the first add-back month, in comparison with the second and third months (Schmidt et al., 2017). While these findings suggest a critical impact of acute variations of both hormones, they do not discern the effect of progesterone from the effect of estradiol (for further details on estradiol effects in PMDD, see Section 4.2.2).

Another intriguing phenomenon in relation to progesterone, or allopregnanolone, is that women with PMDD experience their most intense symptoms in the late luteal phase, when progesterone and allopregnanolone levels are declining, not at the progesterone peak in the mid-luteal phase (Nevatte et al., 2013). Thus, PMDD symptoms are not dose-dependently associated with serum levels of progesterone or allopregnanolone. To explain this phenomenon, it has been hypothesized that women with PMDD more rapidly develop tolerance to allopregnanolone than healthy women, leading to withdrawal symptoms when serum concentrations are declining (Turkmen et al., 2011). For a more detailed description of progesterone withdrawal, see Section 4.3.2.1.

The dose of progesterone may also play a role for the mood symptoms, with studies pointing to an inverse u-shaped dose relationship between progesterone, allopregnanolone and mood. In a sample of postmenopausal women on combined estradiol and progesterone MHT, those with allopregnanolone levels in the luteal phase range reported the most severe mood symptoms, whereas those with lower or higher concentrations seemed to be less affected (Backstrom et al., 2015).

3.2.1.2. PMDD and progesterone receptor modulators. Selective progesterone receptor modulators (SPRM) are drugs that act as antagonists at the PRs. Their use in PMDD may shed further light on pathophysiologic mechanisms. Already in the early 1990s, mifepristone was evaluated for treatment in PMDD in two RCTs (Chan et al., 1994;

Schmidt et al., 1991). The first trial was compromised by the use of single dose administration in the mid-luteal phase, which is too late in the menstrual cycle to have any effect (Schmidt et al., 1991). The second trial, which included only seven women, suggested some symptom improvement although not at the statistical level (Chan et al., 1994). Currently, a second-generation SPRM, ulipristal acetate, has made its way to the market. Depending on the dose, ulipristal acetate is either used for emergency contraception (single dosing), or treatment of uterine fibroids (continuous dosing) (Donnez et al., 2012; Wagenfeld et al., 2013). The low-dose continuous treatment induces anovulation (Whitaker et al., 2014) which, together with PR antagonist action, is a conceptually interesting target for expected symptom relief in women with PMDD. A recent proof-of-concept RCT on ulipristal acetate in PMDD pointed to an effect of PR modulation on the core symptoms (Comasco et al., 2020). Findings from HC RCTs provide further evidence that mood symptoms in PMDD may be modulated by PRs, as outlined in Section 4.3.1.1.

3.2.2. PMDD and estradiol

An early study indicated that women with PMDD are equally sensitive to estradiol add-back as progesterone add-back (during GnRH agonist treatment), suggesting hypersensitivity to both sex hormones (Schmidt et al., 1998). However, subsequent studies have only verified symptom reinstatement with the combination of progesterone and estradiol treatment (Segebladh et al., 2009a, Schmidt et al., 2017), and there is even limited evidence for a beneficial treatment effect of estradiol in women with PMDD (Naheed et al., 2017).

Nevertheless, estradiol seems to play a role in regards to PMDD symptoms as progesterone in combination of a high estrogen dose seems more symptom provoking than progesterone combined with a low estrogen dose (Segebladh et al., 2009a). Given that estrogen is heavily involved in up-regulating PRs (in the brain and elsewhere), an increased availability of estrogen may thus result in a larger number of PRs for progesterone to act upon.

In addition, to evaluating progesterone and estradiol in the framework of PMDD, testosterone-mediated effects have received considerable attention. For example, efficacy has been demonstrated for a treatment combination of estradiol and drospirenone, with the latter having anti-androgenic properties (Rapkin et al., 2007). For further details on HC use in PMDD, please refer to Section 4.3.1.2.

3.2.3. PMDD and allopregnanolone

The question arises whether it is progesterone *itself* or allopregnanolone that provoke the PMDD symptoms (Bixo et al., 2018). Strong evidence for allopregnanolone (rather than progesterone) was provided in a recent randomized controlled trial (RCT) on an endogenous allopregnanolone antagonist, isoallopregnanolone. In women with PMDD who had absolutely no follicular phase symptoms, isoallopregnanolone led to a 75% reduction in overall symptoms during the final treatment cycle (Bixo et al., 2017). Other evidence pointing towards allopregnanolone as symptom-provoking factor includes the treatment response to 5 α -reductase inhibitors, which not only efficiently blocked the conversion of progesterone to allopregnanolone, but also led to a significant reduction in PMDD symptoms (Martinez et al., 2016).

Women with PMDD, in comparison to healthy control women, also appear to have different pharmacodynamic responses to allopregnanolone and its 5 β stereoisomer pregnenolone (Sundstrom et al., 1998; Timby et al., 2016). More specifically, a greater sensitivity to allopregnanolone (measured as greater impact on eye movement velocity) was observed in the luteal phase compared with the follicular phase in women with PMDD, whereas the opposite pattern was seen in healthy controls (Timby et al., 2016). In contrast, women with PMDD were reported to have a reduced sensitivity to pregnenolone in the late luteal phase, with stronger effects in those women with more severe symptoms (Sundstrom et al., 1998). Interactions between pregnenolone and allopregnanolone may explain these contradicting findings, as the

former can act as an antagonist of the latter, which is in line with the efficacy of isoallopregnanolone as treatment for PMDD (Bixo et al., 2017). Thus, while PMDD is commonly associated with alterations in GABA-R sensitivity to allopregnanolone, the direction of this effect remains to be clarified (Bixo et al., 2018).

Taken together, the complex interaction between allopregnanolone concentrations and tolerance and withdrawal mechanisms may help explain why the specific mechanism behind the pathological interaction between GABA function, allopregnanolone and PMDD has not yet been pinned down.

3.2.4. PMDD and GABA

Dysfunction in the brain's GABA system has been shown to be linked to depression and other mood disorders, though it is suspected that the role of GABA in PMDD is unique (Godfrey et al., 2018; Luscher et al., 2011). To develop an accurate understanding of sex steroid-based mood disorders, we must study human females *in vivo*. For the specific purpose of studying GABAergic transmission, several neuroimaging and behavioural methods have been utilised.

Studies using magnetic resonance spectroscopy (MRS) have found variations in levels of GABA both across the healthy menstrual cycle and in atypical populations. The first of these studies reported reduced GABA levels across the menstrual cycle in women with PMDD (Epperson et al., 2002). Furthermore, Epperson and colleagues found that GABA levels overall were increased in the luteal phase compared to the follicular phase in healthy controls. The opposite was found in women with PMDD (Epperson et al., 2002). However, GABA concentration, as measured with MRS, only provides a bulk concentration measurement and it is unclear how these measures directly index functional synaptic inhibition (Stagg et al., 2011). That said, these studies do give evidence for significant functional changes in the human female GABA system over the course of the menstrual cycle (Epperson et al., 2005, 2002).

Simple visual annular grating stimuli can be used to induce oscillations in the brain that are recorded using electroencephalography (EEG) (Muthukumaraswamy and Singh, 2013). In particular, the amplitude and frequency of visually induced oscillations within the gamma range (30–90 Hz) are remarkably sensitive to changes in cortical excitation and inhibition driven by changes in the function of GABA (Muthukumaraswamy, 2014; Magazzini et al., 2016; Lozano-Soldevilla et al., 2014; Campbell et al., 2014) and NMDA/AMPA receptors (Shaw et al., 2015; Muthukumaraswamy et al., 2016). Furthermore, recent research has linked gamma oscillations in the human primary visual cortex to changes in GABA-R density (Kujala et al., 2015). EEG recordings of visually induced high frequency gamma oscillations combined with computational models of cortical connectivity (Sumner et al., 2018), and more recently magnetoencephalography (MEG) demonstrate increases in endogenous GABAergic inhibition and a change in the balance of excitation/inhibition over the menstrual cycle in healthywomen (Sumner et al., 2018). These changes were independent of absolute peripheral hormone concentrations, and as gamma oscillations are related to GABA-R density in the visual cortex, this is considered further evidence for complex GABA-R receptor dynamics across the menstrual cycle (Sumner et al., 2018).

3.2.5. PMDD and serotonin

Finally, while this review is primarily devoted to progesterone, some mentioning of serotonin in the context of PMDD is needed. A role for serotonin in PMDD is predominantly suggested by the fact that serotonin reuptake inhibitors (SSRI) can be used for the treatment of PMDD (Shah et al., 2008). SSRIs are effective for PMS and PMDD, regardless of whether they are used intermittently (i.e., only during the luteal phase) or taken continuously (Marjoribanks et al., 2013). The first sign of treatment relief in women with PMDD occurs as soon as 14 h after drug intake (Landen et al., 2009). These temporal relationships suggest that SSRIs may facilitate serotonin transmission by

increasing synaptic levels of serotonin shortly after the onset of treatment (Landen et al., 2009). In analogy with the human findings, short-term administration of fluoxetine seems to prevent allopregnanolone withdrawal-induced anxiety-like behavior and molecular adaptations of the GABA-R in the diestrus phase of female rats (Lovick, 2013; Devall et al., 2015).

It is assumed that serotonergic drugs affect mechanisms downstream of the primary causal agents for PMDD. Interestingly, SSRIs increase allopregnanolone levels in the brain, rapidly and at low doses, as demonstrated in rodents (Uzunov et al., 1996) as well as in patients with depression (Uzunova et al., 1998; Lovick, 2013). While this has been posited as a putative mechanism behind the efficacy of luteal-phase dosing of SSRIs in PMDD, SSRI treatment in women with PMDD does not change the peripheral allopregnanolone levels (Gracia et al., 2009). Furthermore, this hypothesis has been challenged in view of more recent findings (Bixo et al., 2017).

Of note, in women with PMDD, there are no menstrual cycle phase-specific effects on cerebral binding levels of serotonin transporter and 5HT_{1A} (Dubol et al., 2020). In contrast, animal models of progesterone withdrawal seem to point to a link with various serotonin receptors (e.g., 5HT_{1A}, 5HT₃ and 5HT₇), although the relationships appear to depend on the dose of the antidepressant as well as on the type of the serotonin receptor (Li et al., 2013).

3.3. Additional Hormone-Induced mood disturbances

3.3.1. Mental side effects from hormonal contraceptives

Mental side effects, such as depressive symptoms, irritability, anxiety, and mood swings have become the major reason for discontinuing HC (Lindh et al., 2016). Women who discontinue HC are left with few alternative choices, thus placing themselves at increased risk of unintended pregnancies (Rosenberg and Waugh, 1998; Segebladh et al., 2009b; Skouby, 2010). Thus, understanding and mitigating mental side effects are crucial. As a consequence, HC-induced mood changes have attracted increased scientific attention over the last years (Robakis et al., 2019; Poromaa and Segebladh, 2012; Schaffir et al., 2016; Worly et al., 2018). While the exact number of women who may experience mood symptoms while on HC is still unknown, existing surveys point to around 4–10% (Poromaa and Segebladh, 2012). Outcomes of systematic research overall seems to suggest that effect sizes for HC-induced mood worsening are only small; the great majority of women actually report improved or unchanged mood. More specifically, as of today, only three placebo-controlled randomized HC trials in healthy women exist (Graham et al., 1995; Lundin et al., 2017; Zethraeus et al., 2017). All three suggest minor, yet significant, changes in the negative direction, with increasing anxiety, mood swings, and irritation as well as decreasing sense of general well-being in women allocated to CHC compared to women allocated to placebo (Graham et al., 1995; Lundin et al., 2017; Zethraeus et al., 2017). However, one of the trials (Lundin et al., 2017) reported improved depressive symptoms during the premenstrual phase of the treatment cycle, which is in line with evidence suggesting that hormonal contraceptives can be used to treat PMDD (Lopez et al., 2012; Pearlstein et al., 2005; Yonkers et al., 2005), as further detailed in Section 4.3.1.1.

These data from RCTs are accompanied by outcomes from three large-scale, longitudinal, register-based studies (Skovlund et al., 2016; Zettermark et al., 2018; Slattery et al., 2018) on CHC use and progestogen-only preparation (POP) use and risk of developing depression (measured as filled prescription for antidepressant). It was reported that 0.9 out of 100 HC users are at risk of needing antidepressant treatment for HC-induced mental side effects (Skovlund, 2017). The risk was most pronounced in adolescents as well as in women on long-acting HC (i.e., using patch, vaginal ring, implant and hormonal intrauterine device [IUD]). However, the outcomes of these studies have been met with criticism (Bitzer, 2017): Many women use hormonal contraceptives for medical reasons, such as dysmenorrhea, endometriosis, polycystic

ovary syndrome, acne, PMS, PMDD, or heavy menstrual bleeding. Each of these conditions has been associated with mental health problems, which might be the actual factors that drive the need for antidepressant medication (Sahin et al., 2018; Balik et al., 2014; Gambadauro et al., 2019; Pope et al., 2015; Brutocao et al., 2018; Lukaviciute et al., 2017; Huang and Cheng, 2017; Strine et al., 2005; de Carvalho et al., 2018). Furthermore, there is no biological reason for why the vaginal ring or patch CHC would confer an increased risk compared to an oral CHC. They result in similar, or even lower, serum concentrations of the steroid hormones (Kerns and Darney, 2011; Duke et al., 2007), and comparative RCTs noted no difference in depressive symptoms or well-being between these preparations (Urđl et al., 2005; Sucato et al., 2011). Finally, researchers have also pointed to the absence of dose-response relationships for the POPs, where the low dose hormonal IUD seems associated with higher risks than the higher dosed progestogen implant or injection (Worly et al., 2018).

3.3.1.1. Progestogens cause the mental side effects of HC. Several lines of evidence suggest that the progestogen in the HC causes mood problems: First, one of the placebo-controlled RCTs indicated that mood worsening was only present outside the premenstrual phase (Lundin et al., 2017). That is, when the placebo users were exposed to high endogenous levels of progesterone in the luteal phase, there was no significant difference in mood severity as compared to the CHC users (Lundin et al., 2017). Second, the risk of mental health problems in observational studies is present in the POP users as well (Skovlund et al., 2016; Zettermark et al., 2018). Third, the type of progestogen seems to play a significant role for the surfacing of symptoms during CHC use, where anti-androgenic progestogens seem to be more advantageous than androgenic progestogens (Kelly et al., 2010; Sangthawan and Taneepanichskul, 2005; Bruni et al., 2000; Winkler et al., 2004). Additionally, knowing the lifetime prevalence of mood and anxiety disorders in women, it is presumable that HC-induced mental symptoms may be triggered by preexisting vulnerability. Indeed, in a follow-up study to the RCT by Lundin et al. (2017), it was demonstrated that the HC-related mood deterioration was largely driven by women with preexisting and ongoing mood disorders (Bengtsdotter et al., 2018). Of note, none of the HC RCTs have considered stressful life events, which is a clear limitation in this field of research.

At the same time, allopregnanolone is unlikely involved, as the HC-induced anovulation lead to low allopregnanolone levels (Rapkin et al., 2006), and the metabolites of common HCs, including those with 5 α , 3 α -reduced metabolites, do not have known affinity for GABA-Rs (including LNG and norethindrone) (McAuley et al., 1993; Stanczyk and Roy, 1990). As LNG alters GABA-R plasticity and expression, it has been hypothesized that progestogen-driven alterations in GABA-R expression may change how the brain interacts with the lowered levels of allopregnanolone (Porcu et al., 2012).

3.3.1.2. Hormonal contraceptives in PMDD. Another question is how PMS or PMDD tie into the HC-induced mental side effects. From a clinical point of view, many women who seek medical care for PMDD report they have never tolerated HC, yet CHC offer therapeutic benefit in managing PMDD (Lopez et al., 2012). In particular, low-dose CHCs containing anti-androgenic progestogens have been proven useful in women with PMDD (Lopez et al., 2012; Kim et al., 2015), but also see (Eisenlohr-Moul et al., 2017)). Trials investigating CHCs with androgenic progestogens, on the other hand, have been less successful (Freeman et al., 2012; Backstrom et al., 1992). A potential explanation for the discrepancy between clinical reports and the aforementioned RCTs could be that while women with PMDD experience symptom relief in the luteal phase, they respond negatively to progestogens at other phases of the cycle (Lundin et al., 2017). Scientific attempts to evaluate if PMS or PMDD are risk factors for the HC-induced mood worsening, led to a lack of such links (Lundin et al., 2017), but analyses

were underpowered and as such the existing findings require follow-up in larger samples.

3.3.2. The impact of the postpartum period on mood

Pregnancy appears to have limited detrimental effect on mental health problems, and the prevalence of depression in pregnancy is similar to non-pregnant women (Biaggi et al., 2016). In fact, pregnancy seems to protect against the most severe forms of mental health, such as suicide and hospitalization (Esscher et al., 2015; Munk-Olsen et al., 2009). In contrast, the postpartum period confers an increased risk of depression in comparison with other periods in a woman's life (Vesga-Lopez et al., 2008).

Interestingly, in terms of its neuroendocrine parameters, the normal postpartum period in healthy women can be described as a depression-like state. It is a period of estrogen deficiency (Bloch et al., 2000), progesterone deficiency or withdrawal (Harris et al., 1994), and HPA hypo-activity (Hannerfors et al., 2015; Helligren et al., 2013; Iliadis et al., 2017, 2015, 2016). In addition, the postpartum period is characterized by an increased breakdown of serotonin, norepinephrine, and dopamine (Sacher et al., 2010), and decreased cortical GABA concentrations (Epperson et al., 2006). In terms of its neural correlates (e.g., morphometric measures on brain and brain ventricular size, gray and white matter, as well as brain age), changes in comparison to before or during pregnancy become evident as early as a few weeks (Luders et al., 2020, 2018; Kim et al., 2010; Oatridge et al., 2002) or months (Hoekzema et al., 2017; Lisofsky et al., 2019; Kim et al., 2010). Brain regions undergoing changes postpartum include cortical as well as subcortical areas, some of them involved in mood regulation. In terms of its functional correlates, it was observed that estrogen deprivation in healthy women (as a model of PPD) leads to increased depressive symptoms, which seems to be linked to increased insular activation while processing facial emotional stimuli (Henningsson et al., 2015). Moreover, it seems to be mediated by changes in functional connectivity pertaining to the amygdala as well as hippocampus (Fisher et al., 2017). Last but not least, the estrogen deficiency model has also been associated with a diminished reactivity of the amygdala and insula to monetary rewards (Macoveanu et al., 2016) as well as with a stronger binding of neocortical serotonin transporters (Frokjaer et al., 2015).

Some of these aforementioned biological alterations in postpartum women have been held responsible for impairing women's mental health during the postpartum period, as reviewed in (Skalkidou et al., 2012; Sundstrom Poromaa et al., 2017). However, other factors, such as genetic predisposition, personality traits, and psychosocial factors (just to name a few), are likely to play significant roles.

3.3.2.1. Postpartum blues.

Progesterone and allopregnanolone have been associated with postpartum blues, a transitory state of depressive and anxiety symptoms in the first week after childbirth, thought to affect some 40–50% of women (Rezaie-Keikhaie et al., 2020). Women with a history of PPD seem more sensitive to the postpartum hormonal change as they develop depressive symptoms when high-dose estradiol and progesterone treatment is stopped (Bloch et al., 2000). A greater proportion of women is expected to suffer from postpartum blues than from PMS or PMDD (Turkmen et al., 2011) because the sharp decrease in progesterone concentration after childbirth follows a much longer exposure of GABA-Rs to higher levels of progesterone and allopregnanolone than during a menstrual cycle.

Progesterone withdrawal is likely mediated by allopregnanolone. GABA-active medications, including benzodiazepines, are known to be highly and relatively rapidly susceptible to tolerance and withdrawal effects at the GABA-R. Similarly, tolerance to allopregnanolone after sustained and acute exposure has been demonstrated (Follesa et al., 2001; Birzniece et al., 2006). In addition, after long-term treatment of progesterone or after a pseudopregnancy in female rats, it was shown

that symptoms of anxiety and depression are precipitated once hormones are withdrawn (Smith et al., 2007, 1998a, 1998b; Gulinello et al., 2002). As allopregnanolone has a particular affinity for benzodiazepine insensitive GABA-Rs that contain δ subunits (Smith et al., 2007), allopregnanolone tolerance also has unique consequences for GABA function. Withdrawal from progesterone or allopregnanolone leads to a rapid upregulation of $\alpha 4\delta$ containing receptors (Smith et al., 2007, 1998a, 1998b, Gulinello et al., 2002), which may be instrumental in conferring the progesterone withdrawal-induced mood alterations (Maguire and Mody, 2008). Notably, peripheral GABA-R δ subunit expression increases in pregnant women (Bhandage et al., 2015), and similar changes are noted in the hippocampal tissue of rodents (Maguire and Mody, 2008). Of relevance to postpartum blues is that absence of δ and $\gamma 2$ subunit modulation throughout pregnancy is accompanied by depression- and anxiety-like behavior as well as by poor maternal behavior in mice (Maguire and Mody, 2008; Ferando and Mody, 2013). Moreover, protracted downregulation of δ subunit-containing GABA_A receptor during the postpartum period has been associated with peripartum depression-like behavior in preclinical models. Altogether, as postpartum blues is a risk factor for PPD, this suggests that a maladaptive homeostatic plasticity of GABAergic sensitivity to neurosteroids during pregnancy and postpartum are key contributors to PPD (Mody, 2019; Ferando and Mody, 2013; Maguire and Mody, 2009).

3.3.2.2. Postpartum depression.

The most striking evidence for a role of allopregnanolone in PPD is the development of Brexanolone, in other words allopregnanolone, for treatment of PPD. The safety and efficacy of the 60-h Brexanolone injection has been explored in three RCTs in women with PPD, demonstrating a rapid onset of action and sustained results over a 30-day period (Kanes et al., 2017; Meltzer-Brody et al., 2018). Based on these trials, Brexanolone is now approved by the Food and Drug Administration for the treatment of adult women with PPD. The rationale for testing allopregnanolone for PPD has been described in detail (Walton and Maguire, 2019). However, a deficiency in allopregnanolone levels has not consistently been demonstrated in women with depression during pregnancy or in the postpartum period (Nappi et al., 2001; Helligren et al., 2014, 2017; Osborne et al., 2017; Crowley et al., 2016; Deligiannidis et al., 2013, 2016, 2019). Instead, it has been suggested that the relationship between allopregnanolone and GABA is governed by the same mechanisms underlying PPD (Deligiannidis et al., 2019). Other proposed mechanisms for the effect in PPD include allopregnanolone-induced altered regulation of stress response pathways (Walton and Maguire, 2019). In rats, exogenous allopregnanolone suppresses stress responses through up-regulation of opioid signalling in the brainstem, mimicking the effects of pregnancy (Brunton and Russell, 2011). Rodent studies further suggest that chronic stress, and the resulting HPA axis overload, can cause a depletion of serum as well as brain levels of allopregnanolone. Interestingly, decreased levels of allopregnanolone not only diminish the negative feedback of GABA signaling to the HPA axis, but also its modulatory effect on emotion-regulating brain regions expressing glucocorticoid receptors (Maguire, 2019). Without the balancing effect of an adequate allopregnanolone response, the HPA axis function is thought to deteriorate further. In a series of experiments, Evans and colleagues have confirmed that exogenous allopregnanolone can protect rats against the development of behavioural deficits induced by the social isolation model of depression (Evans et al., 2012). Moreover, the continuous allopregnanolone supplementation also prevented the decline in hippocampal cell proliferation as seen after social isolation (Evans et al., 2012).

Conclusion

In this article, we have tried to collect, organize, and present scientifically solid evidence that progesterone can be a friend as well as a

foe. However, we also aimed to make clear that our understanding of this apparent discrepancy remains poor. Over the course of many decades, we have gained crucial insights into how sex hormones affect the mental health of women, but there is still much to be done. Combined research efforts on the potential of progesterone and its metabolites have led to a new drug for postpartum depression, which is an incredible achievement. However, we still need causal treatment for PMS and PMDD. In the same vein, contraception that women can use without risking mental health problems, is desirable.

To further elucidate the apparently discrepant effects of allopregnanolone in women with PMDD and women with PPD, future studies will need to make comparisons between women with these two disorders and include genetic and epigenetic measures to identify and evaluate risk markers for progesterone (or allopregnanolone) sensitivity. Additionally, given the detrimental impact of adverse mental effects of hormonal contraception, equal attention should be given to study endocrine-psychiatric interactions in healthy women throughout their reproductive age.

Last but not least, we need to acknowledge that, in the field of reproductive endocrinology, there are large differences between species, not only in terms of cyclicality, pregnancy, and delivery, but also in regards to how these events are controlled. Thus, we should exercise caution when extrapolating from one species to another. Without a doubt, animal studies have led to important findings and breakthroughs in humans, but relying on animal models alone is insufficient to capture the fine nuances and complexities of disorders, such as PMDD and PPD. We envision that a possible next step forward is to characterize the GABA system, which may be achieved by carefully designed clinical trials and/or hormonal provocation studies, coupled with brain imaging and neurophysiological methods.

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