Review

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Selecting optimal progestational agents either alone or in combination in common pediatric endocrine settings: challenges of unmet needs

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Abstract: Progesterone is a natural hormone, mainly produced by the corpus luteum, with the foremost endocrine function on the secretory glands of the endometrium. Since being isolated, both natural and synthetic forms have been produced and are utilized for several purposes, including regulating the menstrual cycle and preventing endometrial hyperplasia. Specifically, the use of progestational agents is essential in the treatment of many common endocrine conditions, including polycystic ovary syndrome, congenital adrenal hyperplasia Turner syndrome and functional hypothalamic amenorrhea. Although these agents are essential for disease management, literature that focuses on the benefits of specific progestins as well as the effects on glucocorticoid receptors (GR), mineralocorticoid receptors (MR), and androgenic receptors (AR) is limited. In this review, we provide a disease specific summary of the available literature and highlight where more information is needed.

Keywords: progestin; contraception; polycystic ovarian syndrome; turner syndrome; congenital adrenal hyperplasia

Introduction

Progesterone was first isolated in 1934 from the organic extract of the rabbit corpus luteum by groups investigating its endocrine function. It was not until 1939 that the first synthetic progesterone, referred to as progestin, was synthesized in Germany, a discovery that led to the Nobel Prize in Chemistry that year [1]. Over the coming years, several studies were conducted, and new formulations were proposed for different medical purposes. In 1975, it was recognized that unopposed estrogen replacement therapy was associated with an increased risk of endometrial cancer and that adding progesterone could minimize those risks. Early on, micronized progesterone and suspension in oil filled capsules were first studied. While each form maintains the primary function of progesterone, each progestin has a different constellation of effects based on the alternative receptors, including GR, MR and AR, which are also targeted. These crucial roles of progesterone, as well as the secondary effects, will be discussed in depth throughout this review. In addition, while not the primary focus of this review, the effect of progesterone on bone is worth noting. Physiologically, progesterone seems to promote bone formation and an increase in bone turnover. However, in clinical setting, there are no long-term studies evaluating effects of progestins on bone mineral density in adolescents. For COCs, current literature is suggestive of negative impact on bone mineral acquisition, particularly at lower doses of EE, but the data on fracture risk is lacking [2].

Natural progestational agents

Natural progesterone is produced in the body by the gonads, adrenal glands, brain, and placenta during pregnancy. Regulation of this hormone is by the hypothalamic–pituitary axis via GnRH production and luteinizing hormone (LH) release. Increasing levels of LH stimulate the corpus luteum to produce progesterone during the luteal phase of menstruation. The primary role of progesterone is to stimulate and decidualize the endometrium to develop secretory glands that are ideal for embryo implantation. If a fertilized egg is not implanted, progesterone and estrogen levels fall sharply, resulting in menstrual bleeding.

Natural progesterone is obtained from compound derivatives of soybeans, Mexican yam roots, and occasionally

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from animal ovaries. Interestingly many suspensions of progesterone contain peanut oil and lecithin, which may cause hypersensitivity reactions in patients with peanut allergies. While moringa tree non-nut-based formulations have been studied as an alternative to peanut or lecithin suspensions to reduce allergenicity, no such preparations are currently clinically available [3]. In addition, despite extensive protein binding, the half-life of natural progesterone is only about 5 min [4]. Also, when consumed orally, the natural hormone is quickly deactivated by the digestive system and undergoes hepatic first pass metabolism. Therefore, an oral micronized progesterone (prometrium) was created to increase the half-life and reduce the poor absorption associated with the gastrointestinal tract [5]. Micronization decreases particle size and enhances the dissolution of progesterone, especially when taken with food. Prometrium can be used in a dose of 100–200 mg for 7–14 days for adolescents to induce menses [6]. While the use of Prometrium is common in adults due to its low cancer risk profile compared to synthetic progestins, which have been shown to have an elevated breast cancer risk after long-term use, more studies for its use in adolescents are needed [7].

Different types of synthetic progestins

Progestins are synthetic forms of progesterone that have been modified over the past 80 years. The different formulations have been divided into four generations, based on when they were first synthesized. Another classification divides progestins into estranes, gonanes, and pregnanes based on their structural and chemical properties (Table 1). The structure of each progestin allows for binding to other steroid receptors [8]. Specifically, promegestone, trimegestone, nestorone, and nomegestrol acetate are the most selective agonists of progesterone receptors and are, therefore, associated with the least amount of other steroidal effects [9]. Alternatively, progestins such as levonorgestrel bind to AR and, therefore, have the strongest androgenic effects [10]. Drospirenone has a structure that is similar to that of the aldosterone antagonist, spironolactone, and therefore has a strong antimineralocorticoid and antiandrogenic effects [11]. Generally, 3-mg dose of drospirenone, the amount in a daily pill, is equivalent to 25 mg of spironolactone.

The most common first-generation synthetic progestin is medroxyprogesterone acetate (MPA), which mainly binds to the PR with little cross reactivity. A course of MPA, 10 mg for 7–10 days, is commonly used to mimic the natural progression of progesterone within the menstrual cycle and to stimulate a withdrawal bleed. Injectable forms are also available and used for contraception, referred to as Depo-Provera or depot medroxyprogesterone, although literature that focuses on the use of injectables for endocrine pathology is limited. While MPA has minimal cross-reactivity, there have been studies that suggest an agonistic effect on the glucocorticoid receptor with long-term use. In an *in vitro* study of the relative binding affinity of MPA to GR on human leukocytes, MPA binding was found to be 1.7 times higher than that of cortisol and 6.7 times higher than progesterone, further highlighting the possible coreactivity of MPA and the steroid pathway and possible glucocorticoid effects for patients [12].

Disadvantages/side effects/ contraindications

Progestins have several clinical uses and are often prescribed to adolescents unless another underlying condition precludes their use. The general side effects include gastrointestinal symptoms, breast tenderness, depression, headache, and possible weight gain. Also, acne and hirsutism can occur depending on type of progestin and its androgenicity.

Table 1: Progestins by generation and chemical composition.

	First Generation (Class I) 1950s	Second Generation (Class II) 1960 s	Third Generation (Class III) 1970 s	Fourth Generation (Class IV) 2000 s
Estrane	Norethindrone Norethindrone acetate Norethisterone acetate Ethynodiol diacetate			Nomegestrol acetate
Gonanes	Norgestrel	Levonorgestrel	Gestodene Desogestrel Norgestimate Etonogestrel	
Pregnanes	Medroxyprogesterone acetate			
Other				Drospirenone

In general, the most androgenic progestins are Class II, followed by Class I, then Class III in descending order, while Class IV are antiandrogenic progestins (Table 1). Progestins also pose variable venous thromboembolism (VTE) risk, discussed below. Progestins are contraindicated in subjects at high risk or preexisting breast cancer, cancer of reproductive organs, liver disease, unexplained uterine bleeding, or concomitant with medications for tuberculosis (rifampin), HIV (ritonavir) or anticonvulsants. As for the combined oral contraceptives (COC), according to the U.S. Medical Eligibility Criteria for Contraceptive Use (2016), conditions that represent an unacceptable health risk for COC therapy include breast cancer, cervical cancer, decompensated cirrhosis, migraine with aura, current or high risk of DVT/PE, severe hypertension or vascular disease (systolic>160, diastolic>100), current or history of ischemic heart disease, hepatocellular adenoma or malignant hepatoma, or being less than 21 days postpartum. Women who smoke and are under the age of 35 can generally use COC [13]. While these criteria are typically understood to be for adults, it may be generalized to the treatment of adolescents as well. Progesterone only pills, however, can be used in patients with hypertension and migraine with aura [14, 15].

Historically, the main contributor of VTE risk in COC was determined to be high dose of EE, which was subsequently reduced and the VTE risk was significantly lowered. However, over the years, progestin compounds have also changed with respect to its binding to androgenic and other receptors besides progesterone receptor. It has been now accepted that progestins can play a role in VTE and the progestin may exert modulatory effect on the procoagulant effect of EE [16]. For example, COC containing levonorgestrel, norethindrone, or norgestimate confer a lower VTE risk (5–7/10,000 women years); COC containing drospirenone, dienogest, and gestodene confer a higher VTE risk (9–12/10,000 women years). For reference, the VTE risk in otherwise healthy nonpregnant women is 2/10,000 women years and 20/10,000 women years in pregnant and postpartum women [17]. Continued vigilance and further studies are needed to not only establish the mechanism of VTE but also to develop newer combinations with better safety profiles.

Selection of optimal progestational agent in common endocrinologic conditions in adolescents

Progestational agents are commonly used for amenorrhea or dysfunctional uterine bleeding. However, the use of progestins either alone or in combination with estrogens for several endocrinological conditions in adolescents, including PCOS, CAH, hypergonadotropic hypogonadism (Turner syndrome, premature ovarian failure etc.), hypogonadotropic hypogonadism (congenital hypogonadotropic hypogonadism, hypothalamic amenorrhea, congenital and acquired panhypopitutarism), and androgen insensitivity syndrome, are poorly explored. We sought to review these conditions in adolescents for choice of progestins as most appropriate and optimized for their medical conditions, including comorbidities or associated risk factors (Table 2).

Polycystic ovarian syndrome (PCOS)

PCOS is a syndrome of ovarian dysfunction and hyperandrogenism. Because this is a condition of anovulation, subjects with PCOS are in a chronic state of low progesterone. Its clinical manifestations include menstrual abnormalities and signs of hyperandrogenism, such as increased hair growth and acne with or without obesity [18]. Drospirenone and norgestimate are the two progestins most used in the combined oral contraceptive pill (COC) treatment of PCOS. Drospirenone has antiandrogenic properties and mild diuretic effects, making it an ideal treatment of the hirsutism and the weight changes that are prevalent [19–21]. However, COCs containing drospirenone may be associated with a small increase in the risk of VTE compared to COCs containing levonorgestrel, though this needs to be further studied [22, 23]. Also, third-generation progestin norgestimate is found to have a safer vascular profile, similar to that of the second-generation progestin levonorgestrel [24, 25]. Particularly, norgestimate has also been found to inhibit 5-alpha-reductase and retains peripheral antiandrogenic activity [26]. COCs containing norgestimate have specifically been shown to treat symptoms associated with PCOS such as acne and hirsutism [27, 28]. However, in many instances, additional treatment may be required to control the acne and hirsutism. Alternative treatments include metformin, laser-assisted hair removal, or spironolactone [29–32]. When choosing a COC, the risks and benefits of each agent should be individualized.

Congenital adrenal hyperplasia (CAH)

CAH is an autosomal recessive genetic condition, commonly caused by a mutation of the 21-hydroxylase gene in the adrenal gland that leads to hyperandrogenism, manifesting as acne, hirsutism, menstrual irregularities, and secondary

Table 2: Summary of various progestational agents and COCs used in common endocrinologic conditions in Adolescents after completion of pubertal induction.

Clinical condition	Associated Condition	Estrogenic agent	Progestational agent	Class of progestin	Benefits of progestin	Side effects of progestin
Hyperandogenism						
Polycystic ovarian syndrome	Acne hirsutism metabolic syndrome	**Oral EE 20–35 µg/d**	**Drospirenon**[a]	IV	↓ Acne ↓ Hirsutism	Variable VTE risk
		Oral EE 20–35 µg/d	**Norgestimat**[a]	III	↓ Acne ↓ Hirsutism	Variable VTE risk
Congenital adrenal hyperplasia	Acne hirsutism	**Oral EE 20–35 µg/d**	**Drospirenone**[bh]	IV	↓ Acne ↓ Hirsutism	Variable VTE risk
		Oral EE 20–35 µg/d	**Norgestimate**[g]	III	↓ Acne ↓ Hirsutism	Variable VTE risk
Hypergonadotropic hypogonadism						
Turner syndrome with primary ovarian failure	Cardiac defects Hypertension Obesity Insulin resistance	TDE 25–100 ug 2 times/wk[C] OR oral estradiol 2–4 mg/d[C]	Micronized P 100 mg/d × 10–14 days [C]	Natural P	Lower breast cancer risk long term Generally well tolerated	Nausea Bloating breast tenderness Headache Dizziness Peanut allergy
		TDE 25–100 ug 2 times/wk[g]	MPA 10 mg/d × 10 days[g]	I	Generally well tolerated	GI issues Breast pain Abdominal pain
		Oral EE 20 –35 µg/d	**Norgestimate**[g]	III	↓ Acne ↓ Hirsutism	Variable VTE risk
		Oral EE 20 –35 µg/d	**Levonorgestrel**[g]	II	↓ VTE risk	↑ Acne
		Oral EE 20 –35 µg/d	**Norethindrone**[g]	I	↓ VTE risk	↑ Acne (intermediate between class II&III)
Hypogonadotropic hypogonadism						
Congenital/acquired hypogonadotropic hypogonadism		TDE 50 – 150ug 2 times/wk[d] OR oral estradiol 2–4 mg/d[d]	MPA 10 mg/d × 10 days[d]	I	Generally well tolerated	GI issues Breast pain Abdominal pain
		TDE 25 – 100ug 2 times/wk[g]	Micronized P 100–200 mg/d × 10–14 days[g]	Natural P	Lower breast cancer risk long term Generally well tolerated	Nausea Bloating breast tenderness headache Dizziness Peanut allergy
		Oral EE 20–35 µg/d	**Norgestimate**[g]	III	↓ Acne ↓ Hirsutism	Variable VTE risk
		Oral EE 20–35 µg/d	**Levonorgestrel**[g]	II	↓ VTE risk	↑ Acne
		Oral EE 20–35 µg/d	**Norethindrone**[g]	I	↓ VTE risk	↑ Acne (intermediate between class II & III)
Functional hypothalamic amenorrhea	Weight loss Low BMD	TDE 100 ug 2 times/wk [e]	MPA 2.5 mg/d × 10 days[e]	I	Generally well tolerated	GI issues Breast pain Abdominal pain
		TDE 25–100 ug 2 times/wk[g]	MPA 10 mg/d × 10 days[g]	I	Generally well tolerated	GI issues Breast pain Abdominal pain

Table 2: (continued)

Clinical condition	Associated Condition	Estrogenic agent	Progestational agent	Class of progestin	Benefits of progestin	Side effects of progestin
		TDE 25–100 ug 2times/wk[g]	Micronized P 100–200 mg/d × 10–14 days[g]	Natural P	Lower breast cancer risk long term Generally well tolerated	Nausea Bloating breast tenderness headache Dizziness Peanut allergy
OTHER						
Complete angrogen insensitivity syndrome	No uterus Low BMD	TDE 25–200 ug 2 times/wk[f]	None			
		Oral estradiol 2–4 mg/d[f]	None			

P, progesterone; EE, ethinyl estradiol; TDE, transdermal estrogen; MPA, medroxyprogesterone acetate; VTE, venous thromboembolism. [g]Reasonable other choices. [h]Drospirenone containing CoC cannot be used in any cases of CAH, with mineralocorticoid deficiency. Bold, combined oral contraceptives (CoC) pills (single preparation); others are individual agents. [a][48, 49]; [b][30]; [c][35]; [d][50]; [e][44]; [f][46].

PCOS. Thus, addition of COC may be required to reduce androgen excess in addition to glucocorticoid and mineralocorticoid, but it should not be used as an alternative to glucocorticoid and mineralocorticoid therapy in classic CAH. In contrast to the hyperandrogenism seen in PCOS, CAH is associated with high progesterone along with androgen excess, which prevents ovulation and leads to secondary PCOS.

The most recent congenital CAH practice management guidelines from the Endocrine society, published in 2018, suggest that COC with drospirenone can be effective in reducing both adrenal and ovarian androgen synthesis with no effect on blood pressure or biochemical parameters such as cortisol, renin, or potassium [33]. However, it should be noted that the studies that measured the effects of drospirenone utilized a small number of patients, all without CAH [34, 35]. In fact, there are no recent studies of drospirenone use in adolescents with CAH. Also, it was previously noted that drospirenone has antimineralocorticoid activity and should be avoided in those on Florinef replacement [36] Thus, while carefully selecting the progestational agent for COC, those with minimal or no androgen activity, such as Class III agents, may be favorable at least for those with classic CAH. In milder forms of CAH (e.g., nonclassic CAH with preserved mineralocorticoid activities), drospirenone may offer advantages; however, more studies are needed. Also, the adjunct therapy for hirsutism with spironolactone is relatively contraindicated in classic CAH, as it will cause MR antagonism in these already deficient patients and can lead to volume depletion [37]. However, spironolactone can be used in nonclassical CAH without any untoward effects [38].

Hypergonadotropic hypogonadism: Turner syndrome (TS)

Turner syndrome is a condition associated with ovarian dysgenesis. These patients require hormone replacement therapy to induce puberty and for continuation [39]. It is important to consider the increased risk for hypertension, aortic dilation, and dissection in patients with TS when choosing the appropriate progestational agent [40]. While newer guidelines are being developed, the last published guidelines for management of girls and women with Turner syndrome suggest that progestin supplementation should begin after 2 years of transdermal estrogen (25-100 μg two times per week) or once a withdrawal bleed occurs to allow for normal breast and uterine development [41–43]. At this time, estrogen and progestin are given in a combined sequential regimen, with 21–25 days of estrogen and 1–14 days of progestin. Although there is a lack of data that focuses on adolescents, micronized progesterone or MPA is most favorable due to a decreased risk of VTE [44] and breast cancer [7] risk compared to more androgenic progestins. Regarding cardiovascular risk, there are no studies in adolescents comparing different progestational agents. However, one study in adults compared micronized progesterone to MPA with transdermal estrogen in cases of primary ovarian failure or early menopause and found that micronized progesterone had a more favorable effect on traditional surrogate markers of cardiovascular health [45]. As adolescents reach young adulthood, a COC can be considered [39]. Due to the elevated risk of cardiovascular disease, insulin resistance, and obesity in those with Turner syndrome,

third-generation progestins such as norgestimate may be preferable due to the lower thromboembolic risk. Other possible choices include COCs containing levonorgestrel or norethindrone. These agents should be prescribed with caution, considering the associated comorbid conditions.

Hypogonadotropic hypogonadism (HH): congenital HH

Congenital hypogonadotropic hypogonadism, caused by deficient production, section, or action of gonadotropin releasing hormone (GnRH), is another condition that requires long-term estrogen and progesterone supplementation in girls [46]. Like the treatment of Turner syndrome, transdermal estrogen is started at low doses to mimic natural estradiol levels during gonadarche. Dosing is slowly increased over 2 years until uterine growth and development is optimized, at which point cyclic MPA/micronized progesterone is added. According to the Endocrine Society clinical practice guidelines for patients with panhypopituitarism, COCs may be more acceptable for adolescents, although reasons for this are not cited and further studies comparing various COCs vs. hormonal replacement therapy in this population are lacking [47]. This highlights an important area for further research. The progestin of choice of COC for these patients can be norgestimate, levonorgestrel, or norethindrone, as per individual therapeutic decision.

Hypogonadotropic hypogonadism: functional hypothalamic amenorrhea (FHH)

Functional hypothalamic amenorrhea is defined as the absence of menstruation due to suppression of the hypothalamic pituitary axis. The goal of pharmacological hormone treatment in this condition is to promote bone mineral density. Bone outcomes may be compromised even after 6–12 months of amenorrhea, and thus clinicians may consider short-term hormone replacement therapy if nutritional, psychological, and exercise-related interventions are ineffective in this time period. Current guidelines recommend using TDE therapy (100 µg twice weekly) with cyclic short-term oral MPA(48). The optimal type of estrogen replacement and dose for bone and other tissues deserves further study.

Complete androgen insensitivity syndrome (CAIS)

Patients with CAIS have a female phenotype but an XY karyotype due to a mutation in the AR. Management, therefore, should include comprehensive counseling and full disclosure of the functional, sexual, and psychological issues that may arise [49–51], Patients with CAIS do not have a uterus. Therefore, while they require estrogen replacement for adequate bone development, progestin therapy is not required [52]. Berteloni et all suggest using TDE (25–200 µg twice weekly) or oral estradiol for medical management [53]. Interestingly, a recent study of 26 patients with CAIS, ages 18–54 years, found that testosterone therapy is well tolerated and as safe as estrogen for hormone replacement therapy, especially for those with reduced sexual function [54]. Additional treatment options include gonadectomy and genetic counseling based on the patients' individual goals.

Conclusions

Progesterone is an important hormonal modulator, with the primary role of stimulating the endometrium to develop secretory glands. Because oral progesterone is not well tolerated, synthetic progestins with similar properties have been developed and are important in the treatment of common endocrine conditions. In addition to progestational effects, these progestins have varying degrees of affinity to the GR, MR, and AR, and it is important to consider the potential side effects of these medications, including thromboembolism and androgenic effects. In this paper, we provide a literature based, as well as anecdotal, guidance for progestin use. Often, there is no one progestin type that is without challenges. Therefore, the use of progestational agents in girls must be individualized, taking into account the individual risk factors and needs of the specific patient. In addition, this field requires further studies to fill the gaps in knowledge that will aid in development of treatment guidelines based on stronger and more comprehensive evidence.

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