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Review of Hormone Replacement Therapy in Girls and Adolescents with Hypogonadism

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Abstract

Girls with either hypo- or hypergonadotropic hypogonadism need treatment with estrogens to initiate puberty and maintain normal hormonal mileau. The focus of this review is hormone replacement treatment in girls with hypogonadism, both to initiate and progress through puberty, and to maintain healthy hormonal mileau in women. It also addresses what is known in the literature regarding estrogen levels in girls and women, instructive cases, practical tables for reference and application, and thoughts on future directions in this area. It represents a thorough literature review with author opinions and recommendations.

Girls with normal ovarian function begin puberty on average at 10.5 years old, although there is variation by ethnicity and degree of excess weight gain. The aim of estrogen therapy to initiate puberty is to mimic normal onset and rate of progression. Based on currently available literature, once a diagnosis of hypogonadism is established, we recommend initiating treatment between age 11 to 12 years of age, with dose increases approximately every 6 months until adult levels are reached. In some situations, treatment may be delayed to allow time for diagnosis or permit more time for linear growth, or address unique risks found in girls treated for various cancers or blood disorders. Once adult dosing is reached, progestins are added to protect uterine health. This can be combined sequential, allowing regular menstruation, or combined continuous when menstrual bleeding is not preferred. Treatment is continued until the average age of menopause, again with various considerations for longer or shorter duration based on risk benefit ratios.

Transdermal estrogens are considered the most physiologic replacement and theoretically may have less associated risks. We review what is known about risks and outcomes and areas for future research.

Background

Girls with either hypo- or hypergonadotropic hypogonadism need treatment with estrogens to initiate and promote progression of puberty. The differential diagnosis of hypo- and hyper-gonadadotropic hypogonadism is listed in Table 1. Estrogen treatment recommendations are the same for all diagnoses, with some minor caveats discussed below. However, the gynecologist should be careful to complete all diagnostic testing before initiating hormonal treatment, as diagnosis affects other aspects of care.

Table 1 also lists the differential for functional hypogonadism for completeness. These conditions require treatment of the underlying disease, and it may or may not be appropriate to temporarily treat with hormones based on the patient's age, prognosis, and confounding risk factors. For example, a teenage girl with anorexia nervosa may or may not benefit from the initiation of estrogen while her psychological well-being is treated. Another example is the importance of initiating treatment in an older teenager with decreasing bone mineral density associated with a prolonged course and delayed diagnosis of inflammatory bowel disease. Estrogen treatment in both cases is indicated for bone health, even if ovarian function is predicted to resume in the future.

An understanding of the hypothalamic-pituitary-ovarian axis and its regulation is important for assessing hormone levels at diagnosis and for monitoring of treatment. When the ovaries are absent or not functioning, there is no estradiol (E2) negative feedback on the hypothalamus or pituitary, so luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels rise above normal indicating ovarian failure (1,2), and hence the term hypergonadotropic hypogonadism.

Low anti-Müllerian hormone levels (< 4 pmoL/L) may also predict ovarian failure (1,3). In the case of hypopituitarism or hypothalamic dysfunction, LH and FSH are low, and therefore no ovarian stimulation and no production of E2, and hence the term hypogonadotropic hypogonadism.

Hypogonadotropic hypogonadism is indistinguishable from the normal prepubertal state in young girls and difficult to differentiate from constitutional delay of development in older girls. If there is no definitive diagnosis prior to treatment initiation, it is important to suspend treatment at some point to confirm the diagnosis and establish the need for lifetime treatment.

Girls without breast development by 13 years of age or without menstruation by 16 years of age should be considered for evaluation (4). Adolescents with normal progression of puberty and secondary amenorrhea should also be evaluated.

Estradiol and gonadotropin levels in girls and women

The laboratory assays for estradiol, LH and FSH have improved greatly over recent years, but normative data with the best assays is still scarce. Interpretation of hormone levels is assay dependent. Even with the newest assays, there is still a wide range and overlap between prepubertal and pubertal levels, and across stages of puberty. With that caveat, we review what is reported in the literature regarding normal E2, LH and FSH levels in girls and women, and suggestions for values suspicious for hypogonadism, and levels helpful during treatment.

GnRH testing has not proved helpful in the diagnosis of hypogonadotropic hypogonadism, as no testing criteria to date have achieved good discrimination, and the studies showing some separation have only been done in boys. The long GnRH stimulation test with administration of

repetitive pulses of GnRH over 36 hours shows some discrimination, but is very complicated and invasive and there is significant overlap between patients with constitutional delay and those with hypogonadism (5-7).

GnRH testing is helpful to establish the onset of puberty. A predominant LH over FSH response after GnRH stimulation or peak LH levels of 5 to 8 IU/L (depending on assay) suggests onset of central puberty (8).

The highly sensitive assays for gonadotropins include immunofluorometric (IFMA), immunochemiluminescence (ICMA), and electrochemiluminescence (ECL). In general, LH is a better marker of pubertal initiation than FSH, and FSH is a better marker of gonadal failure than LH (8). Random LH levels > 0.6 IU/L (IFMA) or > 0.3 IU/L (ICMA, ECL) are considered pubertal, but there continues to be a wide range of overlap with prepubertal values (8-11) (Table 2). FSH levels are lower in women with ovulatory and anovulatory follicle development compared with those in women with no follicle development (26.4 ± 7.7, 62.2 ± 19.6 and 182.8 ± 16.3 IU/liter, respectively; $P < 0.001$). Inhibin A levels were also significantly lower in women with no follicle development (12).

Prior to pubertal onset estradiol levels are in general < 15 pg/mL (≤ 58 pmol/L) by RIA or ELISA and < 2 pg/mL (< 7.3 pmol/L) by GCMSMS (10,11). The newer liquid (LCMSMS) and gas (GCMSMS) chromatography-tandem mass spectrometry assays for steroid hormones are more helpful in understanding estradiol levels in children as well as opening the possibility for monitoring levels on treatment (13). Monitoring levels on treatment is not yet standard of care secondary to the paucity of data. The GCMSMS assay correlated well with RIA, indicating its

robustness, but had much lower sensitivity in girls and boys (14). The limit of detection for estradiol by GCMSMS was 2 pg/mL (7.3 pmol/L), and girls prior to breast development had levels < 2 – 7 pg/mL (< 7 - 25 pmol/L). At onset of breast development, estradiol increased to 6 – 45 pg/mL (22 -165 pmol/L), and by end of puberty levels ranged 89 – 778 pg/mL (326 – 2856 pmol/L).

The normal range of estradiol in cycling women is very wide as determined by conventional assays (Table 2), with early follicular phase levels as low as 20-40 pg/mL (75 – 150 pmol/L), midcycle peak levels of 200-600 pg/mL (730 – 2200 pmol/L), and luteal phase levels of 33 – 306 pg/mL (121 – 1123 pmol/L) (15). Mauras et al have suggested targeting a mean level of 96 $\pm$ 11 pg/mL (352 $\pm$ 40 pmol/L) in patients with Turner Syndrome, a good model for hypogonadism in women (16).

Treatment options for induction of puberty and maintenance of feminization

The goals of estrogen treatment are to mimic the normal progression of puberty. Estrogen replacement is important for bone, uterine, and psychosocial health (17). The average age of pubertal onset is between 11 – 12 years of age, and therefore we suggest this age for initiating estrogen treatment in girls in whom a diagnosis of hypogonadism is known.

If the diagnosis is unclear or a simple delay in puberty is suspected (For example, in a family with a history of significant pubertal delay, or in a healthy athlete), estrogen treatment can be delayed slightly longer. If the diagnosis is still not confirmed, treatment may start and testing can be done off treatment at a later date (Figure). In cases of hypergonadotropic hypogonadism,

once gonadotropins are elevated, it is appropriate to consider estrogen treatment between 11 – 12 years of age, with the goal of not delaying pubertal onset beyond age 14 years. The authors note that there is a lack of data regarding the optimal age range for initiation of estrogen treatment. Recommendations are based on the average age of pubertal onset and the risks to uterine and bone health of delayed onset. A retrospective study of 76 girls with Turner Syndrome demonstrated that delay in estrogen therapy to 15 yrs was an independent risk factor for lower bone density (18). There are also published associations between later age of menarche and increased risk of fracture and post-menopausal osteoporosis (19-29). A girl with a family history of menarche at age 10 years old and good height outcome may initiate treatment earlier than a girl with a family history of later menarche or a girl with other concerns.

Treatment should be initiated at low doses to mimic normal puberty and preserve growth potential. Increases in dosing at 6 month intervals can mimic the normal pubertal tempo until adult dosing is reached. The starting dose is theoretically about 10% of adult dosing (30), and is increased by about 100% every 6 months for 4 dose changes over a 2 - 3 year period. However, no studies to date have rigorously studied outcomes in relation to the rate of dose increase for the different preparations and the different diagnoses.

Estradiol (E_2) is the natural form of estrogen that is secreted and binds to the estrogen receptor in humans (31). Ethinyl estradiol (EE) is a synthetic E_2 analogue that is not metabolized to E_2 and therefore is not detectable using commercial estradiol assays. Conjugated equine estrogens (CEE)(ex: Premarin) were commonly used, but more recent data suggests increased risk of thrombophlebotic phenomenon and stroke with these preparations (32-34). Estrogens are metabolized in the liver mostly by microsomal cytochrome P-450 (35-37).

Theoretical benefits of transdermal E_2 to initiate puberty and maintain adult levels include the more physiologic route of delivery, avoiding first-pass effects in the liver (38), and decreased risk of stroke (39,40). However, there is no study to date of transdermal use from initiation of puberty until adulthood.

Table 3 lists commonly available, lower-dose estrogen preparations for pubertal induction, and considerations for their use. **Table 4** lists some common progestin and estrogen/progestin combination replacement options after pubertal induction is complete (41). In general, the regimens listed in Table 3 result in onset of breast buds within 6 months, and stage 4 breasts in 2.25 years, on average, in most girls (42-46).

The most common form of hypergonadotropic hypogonadism is Turner Syndrome, which is a good model for treatment, although the risks of treatment may differ among etiologies. Girls with Turner Syndrome are short and often treated with growth hormone so there can be a need to balance height outcome with the desire for more rapid feminization. Addressing this balance will affect the dose and timing of E2 treatment. When height is a concern, E2 treatment may be started later or dose increased more slowly.

In girls who have a uterus a progestin must be added once breakthrough bleeding occurs, or after 2 years of adult dose E_2 treatment, to minimize irregular bleeding, endometrial hyperplasia and the risk of endometrial cancer associated with unopposed estrogen (47,48). **Table 5** lists the classes and generations of progestins available (49). Each progestin exerts unique effects based on its affinity for the progesterone, glucocorticoid, mineralocorticoid, and androgen receptors. Choices for use include those effects listed in Table 5. In adult women, crystalline progesterone, like Prometrium®, is preferred based on decreased cancer risk (48), however no data are

presently available on the use of this in young girls with hypogonadism. The combined oral contraceptives (OCs) containing an estrogen and a progestin are commonly used for convenience. These may only be used once pubertal development is complete, as dosing is too high for pubertal initiation. All OCs increase the risk of venothrombotic episodes (VTEs), although some to lesser degree than others (50) including: desogestryl, norgestimate, gestodene, or drosperinone. Micronized progesterone is also associated with a lesser risk (51).

Regimens of estrogen plus a progestin can be either combined-sequential with an estrogen for 21-28 days per month and the progestin for only 10-14 days per month, or combined-continuous with both sex steroids continuously (52). See Table 4 for examples of timing options and dosages.

Transdermal (TD) E2 dosing

The lowest transdermal estrogen patch dosing available delivers 14 µg/day of E_2, and the most widely used low-dose patches deliver 25 µg/day. In order to deliver lower doses, patches with a matrix design can be easily cut, however patches with a reservoir technology should not be cut. A fractionated patch dose (one-quarter patch of 25 µg dose = approximately 6.2 µg) applied overnight mimicked the normal early morning serum E_2 peak, and fell back to baseline within a few hours of patch removal (46). Again, using Turner Syndrome as a model, transdermal E_2 achieves greater suppression of LH/FSH at lower doses than do oral preparations (16,39,53).

Depot E2 is also available, but often less attractive due to the pain of injections (30).

Individualizing treatment is important, and evaluation of rate of physical changes and patient satisfaction helps dictate dosing, route, and tempo of administration. Compliance is also important, and some girls and women may prefer oral over TD preparations. It is important that girls and women understand that replacement therapy for them, in the setting of no endogenous estradiol, is different than estrogen treatment in women with endogenous estradiol.

Adult transdermal replacement doses of 50 – 150 μg/d or oral replacement doses of 2-4 mg/d of E_2 will often be sufficient to achieve average adult physiologic E_2 levels (16). Oral progestin for 10 days per month (combined sequential approach) or continuous progestin regimens are suggested for girls who have a uterus (54). The estrogen patch can be worn continuously during the 10 days of progestin, or not worn during the progestin days (Table 4). If bleeding irregularities occur or if the patient prefers, a progestin coated intra-uterine device can be used together with either continuous oral or transdermal E_2. This will reduce bleeding irregularities and often abolish bleeding and the need for systemic progestin use.

Duration of sex hormone replacement therapy

Once adult replacement doses are reached, treatment should continue until the time of usual menopause around age 51-53 years, when the risks versus benefits of continuing should be assessed, individualized, and reassessed annually (52,54-56).

Monitoring sex hormone replacement treatment

In women with hypergonadotropic hypogonadism, routine monitoring of serum LH or FSH is not recommended as levels remain elevated in agonadal women until higher than physiologic levels

of estrogen are given (57). Estradiol measurement using a sensitive assay (e.g., LCMSMS) allows titrating dosage if desired, although E_2 levels for optimal linear growth, bone health, uterine health, or psychosocial benefit remain to be determined. It is important to note that ethinyl estradiol is not detected by common assays. Clinical assessment, patient satisfaction, patient age, and, in some cases, residual growth potential are the primary determinants for dose increase.

Adult replacement transdermal doses of 50 – 200 µg/d typically allow women to reach normal adult plasma E_2 concentrations. Oral estrogen doses of 2 – 4 mg of E_2 will result in normal circulating E_2 levels (i.e. approximately 100 – 155 pg/mL (367 - 568 pmol/L))(57) and may lead to normal levels of FSH and LH in some women (57,58). It is important not to treat to one specific dose or E_2 level, but to individualize treatment and consider carefully target tissue response, symptoms and risks, to optimize all the health benefits and minimize the risks.

Risks of hormone replacement therapy

When assessing risk – benefit it is crucial to remember that these females have minimal endogenous sex steroids, so it is a different risk assessment than in women with endogenous sex hormones. In general the risks of not treating outweigh the risks of treatment in most cases.

Low-dose estrogen regimens do not appear to interfere with growth. In children who also have short stature, slow initiation of puberty is important to preserve growth potential.

Although there are theoretical reasons to be concerned about the relative systemic and hepatic effects of oral estrogens, evidence thus far does not indicate detrimental effects of treatment

(16,39,59-66). Beneficial effects of oral estrogens on serum lipids have been demonstrated in women with premature menopause and include reductions in LDL-C and elevation in HDL-C (67-69).

Maintenance of bone health is crucial for women with hypogonadism. Delaying estrogen replacement is deleterious to bone health (43, 70, 71). Transdermal estradiol in women with premature ovarian failure is reported to have a more favorable effect on BMD than oral contraceptive pills. (72-75).

Uterine volume is influenced by route, dose, age at onset of treatment, and duration of treatment (43,45, 76-80). The longer the duration of treatment and the higher the dose of estrogen, the better the chances of normalizing uterine size, which is important only if pregnancy options are pursued (81).

Several studies have shown increased thromboembolic risk using oral preparations compared to TD, especially in women with other existing risk factors such as obesity (82). E_2 replacement therapy, oral or transdermal, lowers blood pressure (32-34), whereas EE-containing contraceptives raise blood pressure unless containing an anti-mineralocorticoid progestin (83).

Recent publications showed no increased risk of stroke with progesterone, pregnane derivatives, or nortestosterone derivatives (40,84). However, norpregnane derivatives were found to increase risk (40).

Summary and Conclusion

In summary, we suggest that estrogen replacement should mimic normal physical and social development for timing and progression of puberty, starting between 11-12 years of age and increasing over 2 – 3 years to adult replacement levels, with adjustments to timing based on underlying diagnosis, height, growth potential, and family history of puberty. This regimen improves socialization, linear and uterine growth, and bone health. When available, low-dose E_2 administered by a systemic route is preferred, starting with half of a 14 μg patch applied weekly and increasing every 6 – 12 months based on response. In girls with a uterus, a progestin should be added when bleeding begins or after 2 – 3 years of adult dose estrogen treatment if no bleeding occurs. When transdermal E_2 is not available, or compliance is an issue, evidence supports use of oral micronized E_2 or depot E_2 preparations. Only when these forms of E_2 are unavailable, should other forms of estrogen be prescribed. Some women prefer the ease of use of an oral combination of estrogen and progestin. Some preparations are safer than others, and the benefit of good compliance to a chosen regimen outweighs the risk of no treatment. Treatment is monitored by patient and physician satisfaction. When hypogonadism is diagnosed later, or develops after initial normal pubertal progression, estrogen dosing regimens can progress more rapidly.

Future Directions

- Optimal route, dosing, and timing regimen for pubertal induction need further study now that more transdermal preparations are available. Outcomes should include pubertal development, uterine growth, bone health, and psychosocial measures.

- Long term risks of estrogen replacement in women without endogenous estradiol need further study, since these may be different from post-menopausal studies.
- Specific LH, FSH, and E2 levels for diagnosis and monitoring of treatment can be studied with newer assays now available.

Disclosure/Conflict of Interest:

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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554 **Figure Legends**

555 **Figure. Flow diagram for initiating estrogens and progestins in girls with a uterus.**

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557 **Table 1. Differential Diagnosis of Hypogonadism**

		Associated Genes	**Major Phenotype**
Hypergonadotropic Hypogonadism			
	Ovarian agenesis/dysgenesis	FSHR	
	Premature Ovarian Failure	MCM9 MCM8 SYCE1 HFM1 STAG3 BMP15 FMR1 AIRE	
	Turner Syndrome		Short stature, web neck, cardiac defects
	Swyer syndrome		46XY with streak gonads and female genitalia
	Galactosemia	GALT	
	Pelvic trauma		
	Infection		
	Surgery		
	Radiation Sequelae		
	Chemotherapy		
Hypogonadotropic Hypogonadism			
	Panhypopituitarism		
	Septo-optic dysplasia	HEX1 SOX2	Visual impairment
	Surgery Sequelae		
	Radiation Sequelae		
	Chemotherapy -Alkalating agents		
	CNS tumors		
	Isolated Hypogonadotropic hypogonadism	many	
	Kallmann syndrome	KAL1 FGF8 FGFR1 CHD7 SOX10	Tall stature, anosmia
	Mutations in LH and FSH β subunits		
	GnRH receptor gene mutations	NR0B1, GPR54	
	Transcriptor factor gene mutations	PROP1, LHX3, LHX4, HESX1,	

		POU1F1	
	Prader-Willi Syndrome	Loss of paternal 15q11.2	Developmental delay, abnormal satiety
	Bardet Biedl	Various genes	Developmental delay, visual impairment, polydactyly, obesity, renal impairment
	CHARGE syndrome	CHD7	Coloboma, heart defect, choanal atresia, short stature, ear abnormalities
	Gordon-Holmes syndrome	OTUD4, PNPLA6, RNF216, STUB1	Cerebellar ataxia, dementia
	Hereditary hemochromatosis	HFE	Cirrhosis, diabetes, cardiomyopathy
	Tubulinopathies	TUBB3	Facial weakness, developmental delay, polyneuropathy, tracheomalacia
	X-linked adrenal hypoplasia	NROB1	Adrenal failure
	Obesity syndromes	PCSK1, LEP, LEPR	Hypocortisolism Morbid Obesity
Functional hypogonadism			
	Systemic/chronic illness		
	Inflammatory bowel disease		
	Celiac disease		
	Hypothyroidism		
	Anorexia nervosa		
	Excessive exercise		

Table 2. Estradiol, LH, and FSH levels by Pubertal Stage

Pubertal Stage	**E2 pmol/L**	**E2 pg/mL**	**LH level IU/L**	**LH level IU/L**	**FSH level IU/L**
1	<2 – 7	1 - 258	<0.6	<0.3	
2	6 - 45	1 - 447	> 0.6	>0.3	
3	37-589				
4					
5	89-778				
Follicular					12
Mid-cycle					
Luteal					
No ovarian function					182.8 + 16.3
Assay	GCMSMS	ELISA	IFMA	ICMA	
Reference	J Steroid Biochem Mol Biol. 2018, Ankarberg-Lindgren	J Pediatr Endocrinol Metab. 2018, Ding	JCEM 1999 Brito	JCEM 1999 Brito	JCEM 2005, Corrine

Table 3. Some common low-dose estrogen treatment options for pubertal induction in Turner Syndrome and considerations for use. *(Reprinted with permission from: Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, Mauras N, Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations, J Clin Endocrinol Metab 2018, 103:1-14.)*

Preparation *	**Doses available, frequency, route**	**Starting dose at puberty**	**Dose Increase approximately every 6 m to adult dosing**	**Consi ns for**
Transdermal options (some brands)		3-7 µg/day	25-100 µg/day	See te applyi patche
Menostar (Bayer) (matrix)	14 µg weekly TD	½ patch weekly	Only used for low dosing, not full replacement	Easies give lo once a dosing
Vivelle Dot (Novartis) (matrix)	25, 37.5, 50, 75, 100 µg twice weekly	¼ patch weekly, or 1 patch per month (no patch other 3 weeks)	25-100 µg twice weekly	Desigr twice v but ca once p to incr dose s
Vivelle Mini (matrix)	25, 37.5, 50, 75, 100 µg twice weekly	Too small to consistently cut	25-100 µg twice weekly	Smalle patch, smalle
Generic (different brands in different countries)	25, 37.5, 50, 75, 100 µg twice weekly	¼ patch weekly, or 1 patch per month (no patch other 3 weeks)	25-100 µg twice weekly	Once a dosing used
Estraderm (matrix)	50, 100 µg twice weekly	Not small enough to initiate puberty	50-100 µg twice weekly	Can't u intiate pubert
E_2 gel Estragel (Ascend) 0.06% Divigel (Vertical) (0.1%)	0.75 mg E_2/pump 0.25, 0.5, 0.1 mg E_2/ pump	0.25 mg/pump	1 pump daily	Only a in som countr the lov
Oral options				

Table 4. Some common progestin and estrogen/progestin combination replacement options after pubertal induction is complete. *(Reprinted with permission from: Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, Mauras N, Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations, J Clin Endocrinol Metab 2018, 103:1-14.)*

Adding Progestin options	Doses available, frequency and route	Not needed to initiate puberty	Add once bleeding occurs or after 2 years	Notes
Medroxyprogesterone acetate	10 mg daily for 10 days		Give with TD E_2, or alone for 10 days	
Micronized progesterone (Prometrium) (AbbVie)	100 mg daily		Give continuously with TD E_2	Less bre cancer long ter
Combined E_2/Progestin sequential patch – some brand options		Do not use to initiate puberty		
Climara Pro (Bayer)	E_2 0.045 mg /levonorgestrel 0.015 mg/24 h		1 patch weekly	
Combipatch (Noven)	E_2 0.045 mg /norethidrone 0.14 or 0.25 mg/24 h		1 patch weekly	
Evo-Sequi (Janssen)	E_2 50 µg /norethisterone acetate 170 µg/24 h		2 patches weekly	
Combined E_2/Progestin sequential pills		Do not use to initiate puberty		
Trisequens (NovoNordisk)	E_2 2 mg /norethisterone acetate 1 mg		1 pill/day	
Divina plus	Estradiolvalerate 2 mg/Medroxyprogesterone acetate 10 mg		1 pill/day	

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Table 5. Classification of Progestins

(Reprinted with permission from: Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, Mauras N, Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations, J Clin Endocrinol Metab 2018, 103:1-14.)

Classification	Progestin	Generation	Other Activity
Natural	Progesterone		Specific progestational, anti-mineralocorticoid
Synthetic			
Pregnane derivatives			
Acetylated	Medroxyprogesterone acetate	1	Glucocorticoid activity
	Megestrol acetate	2	Specific progestational
	Cyproterone acetate	3	Androgenic, Glucocorticoid activity
Nonacetylated	Chlormadinone acetate	1	Androgenic, Glucocorticoid activity
	Dydrogesterone	2	Specific progestational
	Medrogestone	2	Specific progestational
19-Norpregnane derivatives			
Acetylated	Nomegestrol acetate	4	Anti-androgenic
	Nesterone	4	
Nonacetylated	Demegestone	4	
	Promegestone	4	Androgenic, Glucocorticoid activity
	Trimegestone	4	
Nor-testosterone			
Ethinylated Estranes	Norethindrone (norethisterone)	1	Androgenic
	Norethindrone acetate	2	Androgenic
	Ethynodiol diacetate	1	
	Norethynodrel	1	
	Lynestrenol	1	
	Tibolone	1	

13-Ethylgonanes	Levonorgestrel	2	Androgenic
	Desogestrel	3	
	Norgestimate	3	
	Gestodene	3	
Nonethinylated	Dienogest	4	Anti-androgenic
	Drospirenone	4	Anti-androgenic, anti-mineralocoid

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587 **Figure.**

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