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Title:-

Hormone Supplementation For Pubertal Induction In Girls

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SUMMARY

Pubertal induction in girls with ovarian insufficiency aims to mimic normal puberty, a highly complex process. Here we amalgamate the sparse global evidence and propose three options for pubertal induction regimens including oral ethinyloestradiol, and oral and transdermal 17β-oestradiol. The introduction of progestogens is discussed and the transition to hormone supplementation for adult women. The merits and disadvantages of the different options are detailed. The available evidence indicates that transdermal 17β-oestradiol has the most favourable efficacy, safety, and cost profile but randomised controlled trials are urgently required to determine which regimen provides the best clinical outcomes.

INTRODUCTION

Girls with primary or secondary ovarian insufficiency require supplementation with oestrogen to induce puberty. However, there are no licensed hormone preparations for children, resulting in off-label prescribing of formulations licensed for adults. Traditionally, most clinicians in the UK have used low dose synthetic ethinyloestradiol with variable clinical outcomes.[1] More recently, the escalating cost, poor availability and unfavourable outcomes associated with low dose ethinyloestradiol has necessitated the use of alternatives. In continental Europe and USA, there is greater experience of using natural transdermal or oral 17β-oestradiol.[2] Following critical review of the available literature and extensive consultation by a working group of the British Paediatric Endocrine Society (BSPED), this guidance document for pubertal induction has been produced. The document provides the full range of therapeutic options including oral and transdermal 17β-oestradiol and oral ethinyloestradiol.

Pubertal induction aims to achieve normal tempo and magnitude of breast and uterine development and adolescent growth spurt by mimicking the natural pubertal process. These outcomes are achieved with low starting doses of oestrogen which are then gradually increased, whilst monitoring the clinical response in linear growth and breast staging. High dose oestrogen early in puberty or rapid dose escalation may result in reduced final height and poor breast development, such as prominent nipple development with poor supporting breast tissue. There are also concerns that unphysiological supplementation may adversely affect uterine development and bone mass accrual.[3]

Girls are known to prefer progress in tandem with their peers. Therefore, the recommended age for commencing pubertal induction is around 11-12 years, although some girls may actually present much later.

The aims of pubertal induction are to:-

- Allow the natural development of secondary sexual characteristics (particularly breast shape and size).
- Allow normal uterine growth to an adult size and shape.
- Achieve a good adolescent growth spurt.
- Achieve normal peak bone mass.
- Support psychological maturation and adjustment.

LITERATURE REVIEW

There is a real paucity of carefully constructed, randomised controlled clinical trials in girls undergoing induction of puberty. The evidence base is derived mainly from

expert experience, a small number of observational studies and very few controlled trials on small study populations. In addition, studies of treatment acceptability and patient adherence are lacking.

Transdermal/Oral 17β-oestradiol for Induction of Puberty

17β-oestradiol is the most physiological form of oestrogen, being identical to ovarian secreted oestrogen and measurable in serum. Whilst oral 17β-oestradiol is metabolized in the liver to the weaker oestrogen oestrone, transdermal 17β-oestradiol does not undergo this first-pass effect. The available evidence on the use of 17β-oestradiol is sparse on all clinical outcomes mentioned above.

Transdermal 17β-oestradiol

Three regimens using transdermal 17β-oestradiol were reviewed. In a carefully monitored observational study, Ankarberg-Lindgren et al., used a low dose transdermal 17β-oestradiol regimen in 15 girls with primary ovarian insufficiency (POI) which resulted in pubertal development to breast stage 2-3 (B2-3) over a period of 3.5-29 months (median 10 months).[4] However, this dosing regimen was based on body weight with complicated cutting of patches into small fractions and did not extend beyond early to mid-puberty. Davenport provided a regimen for pubertal induction in girls with Turner syndrome basing transdermal 17β-oestradiol dose on body weight in early puberty, and adjusting patch size to target serum oestradiol levels.[5] Nabhan et al. used much higher doses of transdermal 17β-oestradiol starting with 25µg/24hrs.[6]

There is very limited but encouraging evidence on breast development [7], uterine growth [8, 9] and bone accrual [10] in females treated with transdermal 17β-oestradiol. Because of its mode of administration, transdermal 17β-oestradiol does not lower IGF-1 levels since there is no effect on hepatic metabolism.[11] Therefore, it might enhance linear growth although this has not been studied to date.[8]

Oral 17β-oestradiol

Four regimens using oral 17β-oestradiol for pubertal induction were reviewed. Zacharin used a starting dose of 0.5mg 17β-oestradiol every second day, increasing doses over 2 years to an adult dose of 2mgs daily.[12] Delemarre et al.[13] and Bannink et al.[14] based 17β-oestradiol dose on body weight, starting with 5μg/kg/day and increasing to an adult dose over 2 and 3 years respectively. Labarta et al. used 0.2mg 17β-oestradiol daily for one year, followed by 0.5mgs daily for the second year.[15]

In terms of clinical outcomes, Bannink et al. treated 56 girls with Turner syndrome with incremental oral 17β-oestradiol and described normal breast development up to B4-5 in 49 girls (87%).[14] Labarta et al. treated 48 girls with Turner syndrome over 2 years using individualised or fixed dose 17β-oestradiol and described breast development to B4 in 42% and 65% of girls respectively.[15] The results from studies looking at uterine growth are variable.[14, 16, 17] Torres-Santiago et al. found significant but similar improvements in whole-body and lumbar BMD Z-scores over 12 months in 40 girls with Turner syndrome randomised to either oral or transdermal 17β-oestradiol.[18]

Dose titration against serum oestradiol levels

An ultrasensitive assay may be used to monitor serum 17β-oestradiol concentrations in early puberty for both transdermal and oral 17β-oestradiol induction regimens. These results may assist in adjusting doses of oestradiol aiming for serum concentrations in the early pubertal range (10-40pmols/L).[4] Ankarberg-Lindgren et al. showed that standard doses of transdermal oestradiol based on body weight resulted in considerable inter-individual variation in serum 17β-oestradiol concentrations highlighting the clinical value of using serum levels to guide dosing regimens.[19] Conversely, the conclusion from Bannink's low-dose oral 17β-oestradiol study was that serum oestradiol concentrations do not provide additional information on the progression through puberty.[14] For those girls completing puberty, a pharmacokinetic and pharmacodynamic study of oral and transdermal17β-oestradiol in girls with Turner syndrome suggested an adult target 17β-oestradiol concentration of 350pmol/l, as derived from healthy menstruating adult women using integrated mean levels over the natural cycle.[20]

Oral Ethinyloestradiol for Induction of Puberty

Three published regimens for pubertal induction using ethinyloestradiol were reviewed.[13, 21, 22] These regimens share a gradual increase in ethinyloestradiol dose, either from a starting dose of 2μg daily [22] or 0.1 μg/kg/d [13, 21] followed by the addition of a progestogen after 2-2.5 years of unopposed oestrogen.

Ethinyloestradiol is synthetic, cannot be measured in serum, and undergoes first-pass metabolism in the liver. Similar to 17β-oestradiol, published data regarding the clinical efficacy of oral ethinyloestradiol in pubertal induction are very limited.

Suboptimal breast development is reported in girls treated with ethinyloestradiol and oestradiol valerate.[23, 24] However, it is unclear whether this is secondary to problems with the formulation, dose effect, rate of dose escalation or timing of start of therapy.[23] One study of 38 girls treated with incremental oral ethinyloestradiol showed that only 50% developed mature, heart-shaped uterine configurations.[24] Similarly, another study suggested that replacement therapy with ethinyloestradiol gave rise to poor uterine growth and development.[3]

Few studies assessed the effect of ethinyloestradiol on bone mass accrual and there are significant pitfalls in the interpretation of dual energy X-ray absorptiometry results of children and adults with short stature such as in Turner syndrome.[25] A randomised crossover trial in 18 young women with POI showed no significant change in lumbar spine BMD z-score following ethinyloestradiol treatment, raising concerns that this agent may not be effective in increasing bone mass.[10] Another randomised crossover study in 17 young women with Turner Syndrome demonstrated that ethinyloestradiol treatment was associated with high urinary deoxypyridinoline cross-link concentrations, suggesting an unfavourable effect on bone turnover.[26]

Oral ethinyloestradiol is associated with lower IGF-1 concentrations due to its first pass hepatic effect although no studies have compared growth rates and final height using different female hormone replacement strategies. A small synergistic effect on final height was found between low dose childhood ethinyloestradiol and growth hormone treatment in girls with Turner syndrome.[21]

Introduction of Progestogens during Late Puberty

Much of the literature considers the role of oestrogen in pubertal induction with little discussion about the regimen, timing and choice of progestogens.

Progestogens are usually introduced after a suitable duration of unopposed oestrogen (2-3 years) or if more than one episode of significant breakthrough bleeding occurs. Progestogens are usually given in 12-14 day blocks, each inducing withdrawal bleeding. The frequency of blocks may be adjusted according to the patient's wishes, but at least every 2-3 months, which avoids endometrial hypertrophy. Introducing a progestogen too soon, especially using one of the more androgenic agents such as norethisterone, may potentially compromise uterine growth and development.[3]

Options for treatment include oral Utrogestan (200mg once daily) or oral Medroxyprogesterone acetate (5mg once daily). Utrogestan is a natural micronized progesterone which can be given orally and gives good cycle control without significant side effects. Medroxyprogesterone acetate is a synthetic derivative of 17α-hydroxyprogesterone and is less androgenic than derivatives of 19-nortestosterone such as norethisterone.[27]

Oestrogen and Progestogen Replacement Therapy in Adult Women

Adolescent girls undergoing pubertal induction require adult regimens at the end of puberty. Similar to children and adolescents, no product is designed for long term use in women with POI. Options include oral 17β-oestradiol, transdermal 17β-oestradiol, the combined oral contraceptive pill (COCP) and equine conjugated oestrogens (popular in the USA). Typical daily adult regimens for these preparations are oral 17β-oestradiol 2mg daily, transdermal 17β-oestradiol 50-100μg patches

applied twice weekly and left in place until replaced, and COCP daily containing 20-30µg of ethinyloestradiol.

In adult women, progestogen may be given cyclically or continuously depending on whether women wish to experience withdrawal bleeds. Oral progestogens are available either as single agents (e.g. Provera®) or in user-friendly combined packs (e.g. Elleste-Duet®, Elleste-Duet Conti®) or as the COCP (e.g. Microgynon®, Marvelon®). Combined transdermal patches with 17β-oestradiol and progestogen are available, e.g. Evorel Sequi® & Evorel Conti®. However, breakthrough bleeding may be more common in young women using transdermal progestogens.

Unfavourable cardiovascular risk of ethinyloestradiol/COCP

The COCP is cheap (free via the NHS in the UK) and readily available. However, if taken as prescribed on a monthly cycle, women with POI lack oestrogen supplementation 1 in 4 weeks. In addition, the COCP has an adverse cardiovascular and metabolic profile. Specifically, the addition of the ethinyl side chain in ethinyloestradiol induces renin substrate at a much greater rate than natural products and increases the risk of hypertension, particularly in susceptible groups such as women with Turner syndrome.[28] Use of the COCP is also linked with an increased risk of venous thromboembolism.[29] Metabolic studies in adults suggest that ethinyloestradiol treatment gives rise to increased SHBG, decreased IGF-1 and increased insulin resistance.[11] In addition, C-reactive protein and other acute phase reactants may increase which independently predict cardiovascular disease.[30]

Studies comparing transdermal 17β-oestradiol with the COCP demonstrate reduced blood pressure, better renal function and less activation of the renin-angiotensin system in women using 17β-oestradiol.[31]

Women with POI are a heterogeneous group with different risk profiles. Women with Turner syndrome seem to have a reduced risk of breast cancer (relative risk 0.3) whereas women who have had whole body irradiation as conditioning for bone marrow transplantation have an increased risk (relative risk 6.5).[32, 33] Both groups of women are at greater risk of hypertension and Type 2 diabetes than their normal peers and their choice of oestrogen replacement therapy needs to minimise these risks. Women who have had cranial irradiation for brain tumours have an increased risk of stroke and treatment with transdermal 17β-oestradiol is preferred.[34]

Summary of Literature Review

In summary, pubertal induction using oral or transdermal17β-oestradiol is well described but there is some concern regarding appropriate starting doses and inter-individual variation in response. The transdermal route of administration leads to lower peak serum 17β-oestradiol concentrations, lower hepatic metabolism and more stable steady state profiles compared with the oral route.[20] However, transdermal products may be less acceptable to patients. Possibly, the choice of oestrogen matters little at the start of pubertal induction where low dosage is of great importance. While there is good evidence that puberty can be induced too quickly leading to reduced final height, the question whether it can be induced too slowly cannot be answered with confidence.[35] Review of the current literature suggests that for long-term hormone replacement, oral/transdermal17β-oestradiol needs to be

favoured over preparations containing ethinyloestradiol, given their higher cardiovascular risk.

Ultimately, the most important requirement is that girls with ovarian insufficiency are treated with oestrogen in a timely manner and that treatment is continued through to natural menopausal age. Oestradiol deficiency causes cancellous bone loss, endothelial dysfunction, reduced insulin production, abnormal lipid patterns, increased central adiposity and early atheroma.[5] Hence, it is concerning that at a large UK adult Turner clinic, 24% of patients were not receiving oestrogen treatment at all at their first clinic attendance.[36], highlighting the importance of treatment acceptability, adherence and patient education.

Finally, there is very little information on specific dose response (breast and uterine growth and shape, bone accrual, growth) to oral or transdermal 17β-oestradiol and oral ethinyloestradiol, and the bioequivalency of preparations. Estimated daily dose equivalence from the current literature (depending on assays and clinical endpoints) are: **50/100µg transdermal** (applied twice weekly until replaced) **= 2mg oral 17β-oestradiol** (per day) **= 20µg ethinyloestradiol** (per day).[5, 37]

PROPOSED REGIMENS FOR PUBERTAL INDUCTION

Pubertal induction should be individualised taking the girl's and family's views into consideration as well as parameters such as height, age, pubertal stage and co-morbidities. The optimal oestrogen treatment comprising route, drug, and dose increments should be determined for each girl. Amongst the paediatric endocrine community, there is general agreement that oestrogen starting doses for pubertal

induction should be about 10% of adult replacement doses. Following extensive literature review, consultation with external experts and the UK Turner Syndrome support group, we present below optimised regimens for pubertal induction in girls with ovarian insufficiency. All induction regimens will take girls into later pubertal stages (Tanner 3-5) over 2.5 years, following which adult hormone replacement options should be used.

Transdermal 17β-oestradiol

The published regimens for pubertal induction using transdermal 17β-oestradiol were considered impractical to administer and implement.[4-6] Therefore, a pragmatic approach to the transdermal regimen was taken, ensuring the use of low doses of 17β-oestradiol, particularly in early puberty.[12] (personal communication with M Zacharin and T Randell, 2016).

Regimen using 25μg 17β-oestradiol matrix patch (**Table 1**)

Matrix patches are self-adhesive and release approximately 25μg 17β-oestradiol /24 hours. Since the oestradiol is evenly distributed throughout the patch, the patches can be cut to provide the required dose. Practically, patches are cut into ½ or ¼ as more complex divisions would be prone to inaccuracies and impracticable. Unused patch fractions may be stored in their packaging in the fridge for up to one week. The patch (or patch fraction) should be applied to clean dry skin over the buttocks or hips using Opsite® (a transparent adhesive film) if necessary to ensure good adhesion.

Table 1 Regimen for pubertal induction using 25µg/24h 17β-oestradiol matrix patch applied once or twice weekly and left in situ for 3-4 days

Monday to Thursday	Friday to Sunday	Duration (months)
¼ patch	No patch	6
¼ patch	¼ patch	6
½ patch	¼ patch	6
½ patch	½ patch	6
1 patch	1 patch	6

Progress to **adult oestrogen / progestogen replacement therapy**

Oral 17β-oestradiol

Whilst oral 17β-oestradiol is indeed used globally for pubertal induction in various preparations, there is a lack of published evidence. Here, we adopt a modification of the regimens published by Labarta and Zacharin.[12, 15] 17β-oestradiol is only commercially available in 1mg tablets and this regimen involves breaking the 1mg tablets (**Table 2**).

Table 2 Regimen for pubertal induction using 1mg 17β-oestradiol tablets

Dose	Tablets	Frequency	Equivalent daily dose	Duration (months)
0.5mg	½	Alternate days	0.25mg	12
0.5mg	½	Daily	0.5mg	6
0.5mg/1mg	½, 1	Alternate days	0.75mg	6
1mg	1	Daily	1mg	6

Progress to **adult oestrogen / progestogen replacement therapy**

Girls and young women taking natural 17β-oestradiol for pubertal induction may have serum oestradiol levels measured to monitor therapy. Ideally, serum oestradiol

levels should be maintained <50pmols/L during the first 18-24 months of pubertal induction to accelerate linear growth without rapidly advancing bone maturation.[5] However, serum oestradiol levels <60pmols/L are not measurable by most clinical laboratory methods. If a girl seems to be making either too slow or too rapid progress through puberty, ultra-sensitive oestradiol assays should be employed. Such assays are based on liquid chromatography tandem mass spectrometry with limits of detection of 4-8pmols/L.[38]

Oral Ethinyloestradiol

This regimen is derived from Hindmarsh.[22] (**Table 3**) Ethinyloestradiol is not easily measured in serum.

Table 3 Regimen for pubertal induction using 2µg ethinyloestradiol tablets

Dose (µg)	Tablets	Frequency	Duration (months)
2	1	Daily	6
4	2	Daily	6
6	3	Daily	6
8	4	Daily	6
10	5 x 2µg or 1 x 10µg	Daily	6

Progress to **adult oestrogen / progestogen replacement therapy**

Table 4 provides a summary of the suggested oestrogen replacement regimens for pubertal induction

Table 4 Summary of the suggested oestrogen regimens

Months from start of induction	25µg 17β-oestradiol matrix patch (e.g. Evorel® 25)	17-β-oestradiol (Oestradiol valerate) 1mg tablets	Ethinyloestradiol 2 µg tablets
0	¼ patch for 3-4 days, no patch 3-4 days	0.5mg (½ tablet) alternate days	2µg (1 tablet) daily
6	¼ patch all week (change every 3-4 days)	0.5mg (½ tablet) alternate days	4 µg (2 tablets) daily
12	¼ patch for 3-4 days, ½ patch for 3-4 days	0.5mg (½ tablet) daily	6µg (3 tablets) daily
18	½ patch all week (change every 3-4 days)	0.5mg and 1mg alternate days	8µg (4 tablets) daily
24*	1 patch all week (change every 3-4 days)	1mg (1 tablet) daily	10µg (5 tablets) daily
30*	Adult COCP or HRT	Adult COCP or HRT	Adult COCP or HRT

* Progestogens should be introduced only after a suitable duration of unopposed oestrogen (usually 2-3 years) or if more than one episode of significant breakthrough bleeding occurs.

Clinical monitoring of progress for all pubertal induction regimens

To ensure safety and efficacy of the suggested approaches, the following clinical data should be collected (**Table 5**):

Table 5 Clinical monitoring of progress for all pubertal induction regimens

Parameter	Pre-Puberty	During puberty (every 6/12)	Post puberty
Blood Pressure	Yes	Yes	Yes (every 6/12)
Height velocity (HV)	Yes	Yes	Yes (until HV<2cms/year)
Pubertal staging	Yes	Yes	No
Pelvic USS	Yes	No	Yes. Document uterine size and shape
Bone age	Yes	Yes (annually)	No
Bone density scan	No	No	One year post menarche; in case of low size-corrected BMD or non-compliance measure again in 3-5 years

PROGRESSION TO ADULT HORMONE REPLACEMENT THERAPY

A progestogen will be introduced for all patients for 12-14 days every 1-3 months at breakthrough bleeding or after 2.5 years of treatment with oestrogen. The preferred progestogen is utrogestan 200mg once daily. Alternatively, medroxyprogesterone acetate 5mg daily may be used. Norethisterone 5mg daily is available but is more androgenic than the other preparations and is linked to a higher incidence of dysmenorrhoea.

Once a dose of transdermal 17β-oestradiol 25µg/24h, oral 17β-oestradiol 1mg or oral ethinyloestradiol 10µg is reached and the girls are receiving a cyclical progestogen, there are further options for their longer term management as young women.

Transdermal / oral 17β-oestradiol

Transdermal 17β-oestradiol may be continued as a matrix patch or an oestrogen gel (e.g. Sandrena®). Adult doses of transdermal oestradiol via patch vary between 50-100µg/24 hours and adult doses of gel vary between 0.5-1mg oestradiol daily. Some young women may prefer oral medication and there are a number of different proprietary preparations which provide 1-2mg of oral 17β-oestradiol daily according to requirement (e.g. Elleste Solo®).

Many preparations are produced in user-friendly packs with patches/tablets containing oestrogen alone, followed by patches/tablets containing both oestrogen & progestogen combined (e.g. Evorel Sequi® [patch], Elleste Duet® [oral]). Many oral preparations contain norethisterone as the progestogen but in low doses of 0.5-1.0mg. Similarly, the dose of medroxyprogesterone acetate is low in these preparations (1-2mgs).

Women wishing to avoid withdrawal bleeds may be given continuous combined preparations, either transdermal patches (e.g. Evorel Conti®) or oral tablets (e.g. Elleste Duet Conti®). However, women with any residual ovarian function may experience troublesome breakthrough bleeding on these preparations.

In young adult women standard laboratory oestradiol assays are used to monitor serum oestradiol levels, aiming for a target 17β-oestradiol level of 350pmol/l.[20]

Progestogen may also be provided using a levonorgestrel-releasing intrauterine device (e.g. Mirena® coil). It is important to ensure that the uterus is of adult dimensions (about 7.5 x 5 x 2.5cms) by ultrasound before use and girls who are not sexually active may require a brief general anaesthetic for insertion.[39]

Women with any potential residual ovarian function in whom pregnancy is not desired should be counselled about the need for additional contraception if using these preparations.

Combined Oral Contraceptive Pill (COCP)

Advice on the use of the COCP for adult replacement therapy should be guided by a risk assessment as set out by the Faculty of Sexual & Reproductive Healthcare.[40] The contained oestrogen is usually ethinyloestradiol (e.g. Microgynon30®, Marvelon®) although17β-oestradiol is used occasionally (e.g. Qlaira®). In order to maximise oestrogen exposure, girls are advised to take at least 3 packs of pills "back-to-back" to reduce "oestrogen-free" weeks. This has the additional benefit of reducing the frequency of withdrawal bleeds. Preparations can also be taken continuously to avoid withdrawal bleeding although initially there may be some breakthrough bleeding until the endometrial lining is atrophied.

The full scope of oestrogen/progestogen replacement for adult women is beyond the remit of this guideline. It is anticipated that young women with ovarian insufficiency will be reviewed in a Transition clinic alongside an adult Gynaecologist or an adult Endocrinologist and kept under review throughout adult life.

CONCLUSION AND RESEARCH NEEDS

The induction regimens proposed here are based on synthesis of the literature, expert views, consultation, pragmatism and practicability. The evidence suggests that transdermal 17β-oestradiol has the most favourable efficacy, safety and cost

profile. Therefore, this BSPED working group recommends it as first choice for pubertal induction in girls.

Nevertheless, how the essential clinical outcomes (breast and uterine size and shape, final height, bone mass, safety and acceptance) compare between regimens has not been well studied. The lack of randomised controlled studies on pubertal induction in girls needs to be addressed. It is anticipated that prospective collection of data from these proposed regimens will provide valuable information about their efficacy and acceptability.

Pros and Cons of oral/transdermal 17β-oestradiol versus oral ethinyloestradiol for pubertal induction in girls

Pros for oral / transdermal 17β-oestradiol

- 17β-oestradiol is more physiological than synthetic ethinyloestradiol especially when administered transdermally since the first pass hepatic effect is abolished.
- Observational studies suggest that oral or transdermal 17β-oestradiol is effective at inducing puberty. Treatment using transdermal 17β-oestradiol can be individualised and can mimic normal puberty closely.
- Oral 17β-oestradiol tablets and transdermal matrix patches are readily available, cheap and have got a favourable cardiovascular risk profile compared to ethinyloestradiol.

Cons for oral / transdermal 17β-oestradiol

- Transdermal patches may be more difficult to use particularly when cutting patches to small sizes as they may fall off and require tape support.
- Transdermal patches may be less acceptable to girls undergoing pubertal induction, particularly if the patch becomes visible or they have a reaction to the adhesive.
- There is some suggestion of inter-individual variation in response to oral 17β-oestradiol tablets and transdermal patches.

Pros for oral ethinyloestradiol

- Oral ethinyloestradiol has been used extensively for pubertal induction, particularly in the UK & USA.
- The tablet preparations are acceptable and easy to take.
- Millions of women worldwide use ethinyloestradiol in the form of the COCP which has a good safety profile.

Cons for oral ethinyloestradiol

- In recent times, low dose ethinyloestradiol tablets (2 and 10 µg) have escalated in cost significantly. They are no longer always readily available.
- Although effective at inducing puberty, the outcomes may be suboptimal and more physiological agents such as 17β-oestradiol may be preferable.
- Oral ethinyloestradiol is associated with an increased risk of hypertension and venous thromboembolism in adults and this risk may be present also in children.

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REFERENCES

1. Gault EJ, Donaldson MDC. **Oestrogen replacement in Turner syndrome: current prescribing practice in the UK**. *Clin Endocrinol (Oxf)* 2009; **71**(5):753-755.
2. Kiess W, Conway G, Ritzen M, et al. **Induction of Puberty in the Hypogonadal Girl – Practices and Attitudes of Pediatric Endocrinologists in Europe**. *Horm Res Paediatr* 2002; **57**:66-71.
3. Bakalov VK, Shawker T, Ceniceros I et al. **Uterine development in Turner syndrome**. *J Pediatr* 2007; **151**:528-531,e1.
4. Ankarberg-Lindgren C, Elfving M, Wikland KA, et al. **Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls**. *J Clin Endocrinol Metab* 2001; **86**:3039-3044.
5. Davenport ML. **Approach to the patient with Turner syndrome**. *J Clin Endocrinol Metab* 2010; **95**:1487-1495.
6. Nabhan ZM, Dimeglio LA, Qi R et al. **Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study**. *J Clin Endocrinol Metab* 2009; **94**:2009-2014.
7. Piippo S, Lenko H, Kainulainen P et al. **Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome**. *J Clin Endocrinol Metab* 2004; **89**:3241-3247.

8. Illig R, DeCampo C, Lang-Muritano MR et al. **A physiological mode of puberty induction in hypogonadal girls by low dose transdermal 17 beta-oestradiol**. *Eur J Pediatr* 1990; **150**:86-91.

9. O'Donnell RL, Warner P, Lee RJ et al. **Physiological sex steroid replacement in premature ovarian failure: randomised crossover trial of effect on uterine volume, endometrial thickness and blood flow, compared with a standard regimen**. *Hum Reprod* 2012; **27**:1130-1138.

10. Crofton PM, Evans N, Bath LE et al. **Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover**. *Clin Endocrinol (Oxf)* 2010; **73**:707-714.

11. Phelan N, Conway SH, Llahana S et al. **Quantification of the adverse effect of ethinylestradiol containing oral contraceptive pills when used in conjunction with growth hormone replacement in routine practice**. *Clin Endocrinol (Oxf)* 2012; **76**:729-733.

12. Zacharin M. **Pubertal induction in hypogonadism: Current approaches including use of gonadotrophins**. *Best Pract Res Clin Endocrinol Metab* 2015; **29**:367-383.

13. Delemarre EM, Felius B, Delemarre-van de Waal HA. **Inducing puberty**. *Eur J Endocrinol* 2008; **159 (Suppl 1)**:S9-15.

14. Bannink EMN, van Sassen C, van Buuren S et al. **Puberty induction in Turner syndrome: results of oestrogen treatment on development of secondary sexual characteristics, uterine dimensions and serum hormone levels**. *Clin Endocrinol (Oxf)* 2009; **70**:265-273.

15. Labarta JI, Moreno ML, Lopez-Siguero JP et al. **Individualised vs fixed dose of oral 17beta-oestradiol for induction of puberty in girls with Turner syndrome: an open-randomised parallel trial**. *Eur J Endocrinol* 2012; **167**:523-529.

16. Snajderova M, Mardesic T, Lebl J et al. **The uterine length in women with Turner syndrome reflects the postmenarcheal daily estrogen dose**. *Horm Res* 2003; **60**:198-204.

17. McDonnell CM, Coleman L, Zacharin MR. **A 3-year prospective study to assess uterine growth in girls with Turner's syndrome by pelvic ultrasound**. *Clin Endocrinol (Oxf)* 2003; **58**:446-450.

18. Torres-Santiago L, Mericq V, Taboada M et al. **Metabolic effects of oral versus transdermal 17beta-estradiol: a randomized clinical trial in girls with Turner syndrome**. *J Clin Endocrinol Metab* 2013; **98**:2716-2724.

19. Ankarberg-Lindgren C, Kristrom B et al. **Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study**. *Horm Res Paediatr* 2014; **81**:239-244.

20. Taboada M, Santen R, Lima J et al. **Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome**. *J Clin Endocrinol Metab* 2011; **96**:3502-3510.

21. Ross JL, Quigley CA, Cao D et al. **Growth hormone plus childhood low-dose estrogen in Turner's syndrome**. *N Engl J Med* 2011; **364**:1230-1242.

22. Hindmarsh PC. **How do you initiate oestrogen therapy in a girl who has not undergone puberty?** *Clin Endocrinol (Oxf)* 2009; **71**:7-10.

23. Doerr HG BM, Hauffa BP, Mehls O et al. **Uterine size in women with Turner syndrome after induction of puberty with estrogens and long-term growth hormone therapy: results of the German IGLU Follow-up Study 2001**. *Hum Reprod* 2005; **20**:1418-1421.

24. Paterson WF, Hollman AS, Donaldson MDC. **Poor uterine development in Turner syndrome with oral oestrogen therapy**. *Clin Endocrinol (Oxf)* 2002; **56**:359-365.

25. Hogler W BJ, Moore B, Garnett S et al. **Importance of estrogen on bone health in Turner syndrome: a cross-sectional and longitudinal study using dual-energy X-ray absorptiometry**. *J Clin Endocrinol Metab* 2004; **89**:193-199.

26. Guttmann H, Weiner Z, Nikolski E et al. **Choosing an oestrogen replacement therapy in young adult women with Turner syndrome**. *Clin Endocrinol (Oxf)* 2001; **54**:159-164.

27. Darney PD: **The androgenicity of progestins**. *Am J Med* 1995;**98**:104S-110S.

28. Gorrill MJ, Marshall JR. **Pharmacology of estrogens and estrogen-induced effects on nonreproductive organs and systems**. *J Reprod Med* 1986; **31**:842-847.

29. Bergendal A, Bremme K, Hedenmalm K et al. **Risk factors for venous thromboembolism in pre-and postmenopausal women**. *Thromb Res* 2012; **130**:596-601.

30. Piltonen T, Puurunen J, Hedberg P et al. **Oral, transdermal and vaginal combined contraceptives induce an increase in markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weight women: a randomized study**. *Hum Reprod* 2012; **27**:3046-3056.

31. Langrish JP, Mills NL, Bath LE et al. **Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure**. *Hypertension* 2009; **53**:805-811.

32. Schoemaker MJ, Swerdlow AJ, Higgins CD et al.**Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study**. *Lancet Oncol* 2008; **9**:239-246.

33. Mulder RL, Kremer LCM, Hudson MM et al. **Recommendations for breast cancer surveillance for female survivors of childhood, adolescent and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group**. *Lancet Oncol* 2013;**14**:e621-629.

34. Campen CJ, Kranick SM, Kasner SE et al. **Cranial irradiation increases risk of stroke in pediatric brain tumour survivors**. *Stroke* 2012; **43**:3035-3040.

35. Kirk JM, Wickramasuriya N, Shaw NJ. **Estradiol: micrograms or milligrams**. *Endocrinology, Diabetes & Metabolism Case Reports* 2016;1-5.

36. Conway GS, Davies M, Merry A. **Treatment of Turner's syndrome**. *Lancet* 1996; **348**:1590-1591.

37. Isotton AL, Wender MCO, Casagrande A et al. **Effects of oral and transdermal estrogen on IGF1, IGFBP3, IGFBP1, serum lipids, and glucose in patients with hypopituitarism during GH treatment: a randomized study**. *Eur J Endocrinol* 2012; **166**:207-213.

38. Owen LJ Wu CF, Keevil BG. **A rapid direct assay for the routine measurement of oestradiol and oestrone by liquid chromatography tandem mass spectrometry** *Ann Clin Biochem* 2014; **51**:360-367.

39. Plavsic SJ, Pathan B, Honemeyer U et al. **Uterine Lesions: Advances in Ultrasound Diagnosis**. In: Kurjak A, Chervenak FA. eds. *Donald School Textbook of Ultrasound in Obstetrics & Gynecology.* Jaypee Brothers Medical Publishers; 2011: 770.

40. Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologists. **UK Medical Eligibility Criteria for Contraceptive Use**. 2016.