# Guidance Statement: Hormone Supplementation For Pubertal Induction In Girls

**Debbie Matthews, Louise Bath, Wolfgang Högler, Avril Mason, Arlene Smyth & Mars Skae (BSPED Working Group)**

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## I Purpose of guidance

Girls with primary or secondary ovarian insufficiency or delayed puberty, after counselling on the necessity and benefit of female induction of puberty, may be treated with incremental doses of oestrogen for pubertal induction. In the UK most clinicians have traditionally used low dose synthetic ethinyloestradiol for this purpose with variable outcomes [1].

However, in most of Europe and the USA natural 17β-oestradiol is increasingly, used either orally or transdermally. 17β-oestradiol is more physiological than ethinyloestradiol, especially when given transdermally since the first-pass effect through the liver is abolished, and has got a favourable cardiovascular risk profile. Moreover, serum oestradiol levels may be measured for treatment monitoring.

In the UK there have been long periods when ethinyloestradiol has been unavailable rendering pubertal induction using this product unreliable and more difficult to manage. In addition, the cost of low dose ethinyloestradiol has escalated so that many GPs are refusing to prescribe (see Addendum VII). Therefore, it is important to use alternatives to ethinyloestradiol for pubertal induction in the UK. Oral and transdermal17β-oestradiol is readily available in the UK at low cost. Oral 17β-oestradiol is available but tablets contain a minimum of 1mg, roughly equivalent to 10mcg ethinyloestradiol, so tablets need to be cut or dissolved carefully (as solubility may vary between preparations) to reach lower induction doses. Similarly, transdermal matrix patches are available in modest doses which can be cut to provide low doses of oestrogen. The dose can be increased gradually according to clinical response. However, review of the literature suggests a number of different dosage regimens for transdermal oestrogen in several observational studies [2-7]. Accordingly, it was agreed that a guidance document should be produced for pubertal induction in girls giving alternative regimens including oral ethinyloestradiol and oral and transdermal 17β-oestradiol according to best practice as derived from peer-reviewed literature. In addition, we propose the measurement of agreed monitoring and outcome variables to allow close audit and evaluation of the regimens used.

## II Introduction

Girls with primary or secondary ovarian insufficiency require induction of puberty using exogenous oestrogen. In those with an intact uterus, a progestogen is added from puberty stage 4 to allow controlled endometrial shedding or, if a girl chooses, continuous progestogen to induce an atrophic endometrium.

**The aims of treatment** are to:-

- Allow the development of secondary sexual characteristics (particularly breast).
- Allow the growth of the uterus to an adult size and shape.
- Achieve a good adolescent growth spurt.
- Achieve normal peak bone mass by late 20's.
- Support psychological maturation and adjustment.

There are 3 main groups who benefit from pubertal induction

Girls with primary ovarian insufficiency (POI) have hypergonadotrophic hypogonadism with elevated gonadotrophins and low or absent levels of AMH. This group includes girls with gonadal dysgenesis (such as Turner syndrome), girls who have been treated for malignant disease with high dose alkylating agents or abdominal radiotherapy, and rare diseases such as galactosaemia.

Girls with secondary ovarian insufficiency have hypogonadotrophic hypogonadism with low gonadotrophin levels and AMH levels within normal limits. This group includes girls with Kallmann syndrome, multiple pituitary hormone deficiency (incl. post-brain surgery), Thalassaemia, and CHARGE syndrome.

Girls with delayed puberty may also benefit from induction of puberty. This may include girls with constitutional delay in growth and puberty.

Experience has demonstrated that breast development and the adolescent growth spurt are achieved by aiming to mimic the pubertal process in normal girls both in tempo and magnitude. This entails the use of low dose oestrogen at the start of pubertal induction, increasing in small amounts and monitoring clinical response (by reviewing linear growth rate and breast staging). High dose oestrogen early in puberty or the rapid escalation of doses may result in reduced final height and poor breast development with nipple development but poor supporting breast tissue. There are concerns that unphysiological supplementation may also affect uterine growth and development and bone mass accrual. Although girls with Turner Syndrome have been described as having small uteri and low BMD after pubertal induction, it is unclear what the underlying causative factors may be. In terms of uterine growth, there is some suggestion that the timing of the introduction of a progestogen may play an important role [8].

Although slow pubertal progression is important, it is equally clear that most girls wish to keep up with their peers and it is important that pubertal development is timely and easily perceptible by the girls themselves. Therefore the ideal age for commencing pubertal induction is around 11-12 years (although some girls may actually present much later).

## III Literature Review

### a. Effects of Oral/Transdermal 17β-oestradiol

Oral and transdermal 17β-oestradiol are widely used for pubertal induction in girls in Western Europe and USA. A clinical observational study by Ankarberg-Lindgren et al., [3]of 54 girls with POI noted that a carefully monitored, low dose regimen of transdermal 17β-oestradiol resulted in pubertal development to breast stage 2-3 (B2-3) in 3.5-29 months (median 10 months). A further study by Piippo using 17β-oestradiol gel described the development of secondary sexual characteristics to at least B4 in 23 girls [9]. There are very few data on uterine growth in girls treated with transdermal 17β-oestradiol. Ankarberg-Lindgren et al., commented in their study that there were limited data on how oestrogen levels relate to uterine development and they were unable to give recommendations. However, a small observational study by Illig et al., of transdermal 17β-oestradiol for pubertal induction in 9 girls with Turner syndrome showed normal uterine growth and development in 3 girls followed using serial pelvic ultrasound scans [7]. Similarly, a study of young women with POI showed that physiological sex steroid replacement therapy, which included the use of transdermal 17β-oestradiol matrix patches, improved parameters of uterine function [10]. The results from studies looking at the effects of oral 17β-oestradiol are variable with suboptimal uterine development being found in some [11, 12] but not others [13]. A study by McDonnell et al., of 18 girls with Turner syndrome suggested that adequate oestrogen replacement in early to mid-adolescence resulted in normal uterine growth and adult dimensions [13]. Crofton et al., showed that treatment with transdermal 17β-oestradiol matrix patches produced a significant increase in lumbar spine BMD z-score whereas treatment using the combined oral contraceptive pill (COCP) as oestrogen replacement therapy did not [14]. Because of its mode of administration, transdermal 17β-oestradiol does not result in lowering of IGF-1 levels since there is no first pass hepatic effect [15]. Theoretically, transdermal 17β-oestradiol should favour enhanced linear growth although this has not been studied in any detail to date [7].

### b. Effects of Oral Ethinyloestradiol

Ethinyloestradiol is widely used in the UK for pubertal induction in girls [1] but not elsewhere in Europe or USA. Therefore, published data regarding its efficacy are limited. Most comparative studies compare oral 17β-oestradiol or conjugated equine oestradiol rather than oral ethinyloestradiol with transdermal 17β-oestradiol. Suboptimal breast development is described in girls treated with ethinyloestradiol

and oestradiol valerate. 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 [16]. Interestingly, a prospective, randomised, placebo-controlled study by Quigley et al., using low dose ethinyloestradiol in girls with Turner syndrome showed a significant beneficial effect on the onset and tempo of puberty [17]. Paterson et al., showed poor uterine development in girls with Turner Syndrome treated with oral ethinyloestradiol [18]. In 38 girls treated with incremental oral ethinyloestradiol, breast development and uterine length progressed with increasing dose. However, only 50% of girls with complete secondary sexual characteristics had mature, heart-shaped uterine configurations. Similarly, another study by Bakalov et al., suggested that replacement therapy with ethinyloestradiol gave rise to poor uterine growth and development [8].

Oral ethinyloestradiol is associated with lower IGF-1 concentrations due to its first pass hepatic effect although this does not seem to be a major clinical problem. A small synergistic effect was found between low dose childhood ethinyloestradiol and Growth Hormone treatment in girls with Turner syndrome, with the girls treated with both agents reaching a greater final height compared with controls [19].

There are few studies assessing the effect of ethinyloestradiol on bone mineral density during pubertal induction even though it is known that 40-50% of total bone mass is accumulated during puberty [20, 21]. However, a randomised controlled crossover trial comparing oral ethinyloestradiol / norethisterone with transdermal 17β-oestradiol / progesterone in 18 young women with POI showed no significant change in lumbar spine BMD z score following the ethinyloestradiol treatment period [14] raising some concerns that this agent may not be effective in increasing bone mass. Furthermore, a randomised crossover study in 17 young women with Turner Syndrome showed that treatment with ethinyloestradiol was associated with suppressed alkaline phosphatase and osteocalcin levels but not urinary deoxypyridinoline cross-links when compared with oral conjugated oestradiol suggesting a poor effect on bone formation or turnover [22]

### c. Comparison of the use of Oral/Transdermal 17β-oestradiol with Ethinyloestradiol for pubertal induction

One of the main problems with inducing puberty in girls is that there is no licensed product, with treatment frequently using off-label formulations intended for adults.

Transdermal 17β-oestradiol may be given in low doses by using matrix patches which are cut to give the required dose. This has been studied in some detail by Ankarberg-Lindgren et al., [2] who have related the dose of oestradiol produced by the patch fragments to the serum oestradiol concentrations obtained and then compared these with concentrations seen in normal girls going through puberty [23].

Oral ethinyloestradiol is available in low-dose 2mcg tablets which have proved effective in the past but their current poor availability and high cost means that

alternative sources need to be sought i.e. 10mcg tablets which do not divide effectively or dissolve readily and are equally expensive.

There are a number of studies comparing oral 17β-oestradiol or conjugated oestrogen with transdermal 17β-oestradiol. Shah et al., compared transdermal 17β-oestradiol with oral 17β-oestradiol in 20 adolescent girls with hypogonadism and found that transdermal 17β-oestradiol was associated with more effective feminisation than oral oestradiol [24]. Nabhan et al., compared oral with transdermal oestradiol and found significantly greater increases in uterine length and volume in the transdermal group together with a trend towards greater breast development. At the study end, 66% subjects in the transdermal group had a mature uterus (>6.5cms) compared with 0% in the oral group. In addition, treatment with transdermal oestradiol resulted in a significantly greater change in spine BMD at 12 months compared with oral [5]. A study by Taboada et al., examined the pharmacokinetics and pharmacodynamics of oral & transdermal 17β-oestradiol in girls with Turner syndrome and compared these values with normal controls. It was found that transdermal 17β-oestradiol was the more physiological although oral 17β-oestradiol was associated with more beneficial effects on lipids (↓ LDL and ↑ HDL) than transdermal which is only associated with ↓cholesterol [6].

There are very few studies comparing oral ethinyloestradiol with transdermal 17β-oestradiol. Studies in young women with POI using a randomised crossover design comparing the COCP with a combination of transdermal 17β-oestradiol and vaginal progesterone showed a reduction in BP, significantly greater changes in spinal BMD, and improvements in uterine parameters in women being treated with transdermal 17β-oestradiol. [2, 10, 14, 25]. In addition, metabolic studies have suggested that ethinyloestradiol used as adult oestrogen replacement therapy gives rise to increased SHBG, decreased IGF-1 and increased insulin resistance [15, 26]. This may have particular implications for women with combined growth hormone & oestrogen deficiency. In addition, increased CRP and acute phase reactants may be found which independently predict cardiovascular disease [27].

Overall, there is no hard evidence to favour the use of either oral/transdermal 17β-oestradiol or oral ethinyloestradiol for pubertal induction. There are no randomised controlled trials comparing final height, normalisation of breast development, cardiovascular risk or patient satisfaction. However, micronized oestradiol is identical to the natural product of the ovary and is the most physiological form of oestrogen available, and there is a trend towards the use of more natural products. The transdermal route of administration leads to lower peak serum concentrations, lower hepatic exposure and more stable steady state profile compared with the oral route [28]. However, transdermal products may be perceived as more difficult to use or less acceptable than oral products and may be less acceptable to patients. Concordance with medication in this group is most important [29]. In addition, there is very little information on specific dose response to oral or transdermal 17β-

oestradiol and oral ethinyloestradiol, and the bioequivalency of these doses. Summarising equivalent doses (depending on assays and clinical endpoints) from the current medical literature suggests the following daily dose equivalence: **50/100mcg Transdermal** (applied twice weekly and left in situ) **= 2mg oral 17β** (per day) **= 20mcg ethinyloestradiol** (per day) [4, 11, 15, 30-32].

## d. Pubertal Induction Regimen for 17β-Oestradiol

Regimens for pubertal induction need to consider age at onset of female hormone supplementation, starting dose, incremental doses and final dose. In addition, monitoring of response to treatment is an important consideration.

In the past it has been recommended to delay initiation of pubertal induction to optimise final height, particularly in girls with Turner syndrome. However, it has also been recognised that girls with ovarian insufficiency want to keep pace with their peers. There have been suggestions for a "window of opportunity" so that pubertal development can only occur during a certain developmental phase but without convincing supporting evidence [8, 11].

### Transdermal

Ankarberg-Lindgren et al., [2] developed dosing guidelines for transdermal 17β-oestradiol based on the investigation of the nocturnal application of transdermal patches in a limited number of hospitalised patients and compared the oestradiol levels obtained with levels from healthy pubertal girls [23]. They proceeded to carry out a retrospective observational study to evaluate the dosing guidelines which were then modified according to response and for use in a clinical setting [3]. The recommended dosing regimen was based on body weight with complicated cutting of patches into small fractions (eg 1/7, 2/7) and applying the patches overnight initially. Dose adjustment was carried out by measuring serum oestradiol levels using an ultra-sensitive assay or clinical assessment of breast development in those centres without access to an ultra-sensitive assay. The dosing guideline did not extend beyond early to mid-puberty.

Davenport [4] provided a recommendation for pubertal induction in girls with Turner syndrome basing transdermal oestradiol dose on body weight in early puberty, and relating 17β-oestradiol doses to target serum oestradiol levels. The regimen included typical adult transdermal oestradiol doses together with advice for the introduction of progestogens.

In the study by Nabhan et al., much higher doses of transdermal 17β-oestradiol were used with 25µg as starting dose and adult doses of 100-150µg [5].

The practice of basing oestradiol dose on body weight is seen in these regimens, at least in the early stages of pubertal induction. This is justified by the finding of serum levels of 17β-oestradiol which vary directly with the weight of the child [3]. However, it may be noted that Labarta et al., compared the use of fixed versus individualised

doses of oral oestradiol for pubertal induction in 48 girls with Turner syndrome and showed that the fixed dose regimen was not inferior to the individualised dose regimen and both resulted in satisfactory pubertal development [33].

### Oral

Zacharin published a regimen for pubertal induction using oral 17β-oestradiol [34]. This starts with a dose of 0.5mg 17β-oestradiol every second day increasing over 2 years to an adult dose of 2mgs. A progestogen is introduced for 12-14 days every 1-3 months after 12 months.

## e. The Value of Measuring Serum 17β-oestradiol to Guide Dosing Regimens

The medical literature is conflicting regarding the value of using serum oestradiol levels to guide 17β-oestradiol dosing regimens for pubertal induction. Thus, Ankarberg-Lindgren et al., [2] found considerable inter-individual variation in 17β-oestradiol concentrations in the early stages of pubertal induction and used an ultrasensitive oestradiol assay to determine dose adjustments. They found that 17β-oestradiol levels of 24-30pmol/l were seen over a large dose range of 0.05-15mcg/kg but reassuringly, doubling an individual's dose resulted in an approximate doubling of the serum level. They recommend checking 17β-oestradiol levels after the start of treatment and after dose changes [2].

Taboada et al., studied the pharmacokinetics and pharmacodynamics of oral and transdermal17β-oestradiol in girls with Turner syndrome [6]. They provided a target 17β-oestradiol level of 350pmol/l derived from healthy menstruating adult controls using integrated mean levels over the natural cycle. Transdermal 17β-oestradiol doses of 37.5µg and 75µg gave mean serum levels of 140pmol/l and 420pmols/l respectively. Hence, it can be seen that the measurement of serum 17β-oestradiol levels can be used to refine dosage regimens. This is important since the assessment of clinical response can be subjective and open to error. Similarly, the degree of suppression of LH and FSH is variable in POI due to lack of inhibin and cannot be used to monitor progress.

On the other hand Bannink et al., prospectively looked at the effect of low dose oral17β-oestradiol in 56 girls with Turner syndrome and concluded that serum hormone levels do not provide additional information for evaluating the progression through puberty in a clinical setting [11]. It is likely that the usefulness of serum 17β-oestradiol levels is determined by the availability of ultrasensitive oestradiol assays.

## f. Pubertal Induction Regimen for Ethinyloestradiol

Three published regimens for pubertal induction using ethinyloestradiol were reviewed [19] [35] [36]. These regimens are very similar and share a gradual increase in ethinyloestradiol dose in early puberty followed by the addition of a progestogen after about 2 years of unopposed oestrogen. Ross et al. [19] suggested very low doses of ethinyloestradiol in early to mid-childhood to optimise growth. An

adult replacement dose of 30mcg ethinyloestradiol was suggested by Delemarre et al. [36] to be provided as the COCP. Hindmarsh [35] suggested oral or transdermal hormone replacement depending on patient preference and also proposed monitoring of progress every 6-12 months with height velocity, pubertal staging, blood pressure, bone age, pelvic USS and bone mineral density (in later stages of puberty). None of the authors discussed options for choice of progestogens.

### g. Oestrogen Replacement Therapy in Adult Women

It is important to consider full oestrogen replacement doses used by adult women since girls undergoing pubertal induction reach adulthood and require adult regimens. As in children and adolescents, there is no product designed for long term use in women with POI and options include oral 17β-oestradiol , transdermal 17β-oestradiol, the COCP and equine conjugated oestrogens (popular in the USA). Typical daily adult doses for these preparations are oral 17β-oestradiol 1-2mg, transdermal 17β-oestradiol 50-100mcg with patches applied twice weekly and left in place until replaced, and COCP 20-30mcg ethinyloestradiol.

The COCP is readily available and cost effective, and is more acceptable socially in younger women. However, it can give rise to obesity, hypertension and is linked to adverse metabolic profiles. The addition of the ethinyl side chain induces renin substrate at a rate 40x greater than that of natural products and greatly increases the risk of hypertension, particularly in susceptible groups such as women with Turner syndrome [37]. Use of the COCP is also associated with an increased risk of venous thromboembolism [38]. Studies comparing the COCP with transdermal 17β-oestradiol have shown reduced BP, better renal function and less activation of the renin-angiotensin system in women using 17β-oestradiol [25]. Women with POI are a heterogeneous group. Women with Turner syndrome seem to have a reduced risk of breast cancer compared to their normal peers (relative risk 0.3) but women who have had whole body irradiation as conditioning for bone marrow transplantation have an increased risk (relative risk 6.5) [39] [40]. Both groups of women are at greater risk of hypertension and Type 2 diabetes than their normal peers and so it is particularly important to ensure that their oestrogen replacement therapy minimises these risks.

### h. The Introduction of Progestogens in Pubertal Induction

Much of the medical literature considers the important role of oestrogen in pubertal induction with very little discussion about the introduction of progestogens, the timing and choice of these agents.

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. Progestogens are usually given in blocks for a minimum of 12 days but the frequency of blocks may be adjusted according to the patients' wishes, usually at least every 2-3 months, ensuring that there is no evidence of endometrial hypertrophy. There is some suggestion that introducing a progestogen too soon,

especially one of the more androgenic agents such as norethisterone, may compromise uterine growth and development [8].

Utrogestan® is a natural micronized progesterone which can be given orally (200mgs once daily) and gives good cycle control without significant side effects. Alternatively, medroxyprogesterone acetate 5-10mg once daily for 12 days may also be used.

Progestogen can also be administered by the transdermal route and this may be preferable for women who have used patches for pubertal induction. It is available in combined patches with 17β-oestradiol eg Evorel Sequi® & Evorel Conti®. The progestogen may be given continually or cyclically, depending on patient choice. However, breakthrough bleeding may be more common in young women using transdermal progestogens (personal communication M. Zacharin).

### i. Summary of Literature Review

In summary, there is a paucity of carefully constructed, randomised controlled clinical trials looking at pubertal induction in girls. The evidence base is derived mainly from expert experience with a small number of observational studies and very few controlled trials with small study groups. Randomised trials are particularly difficult because of the heterogeneous population, endpoints that are difficult to quantify precisely and the long duration that is required. Pubertal induction using oral or transdermal17β-oestradiol, is well described in observational studies but there is some concern regarding appropriate starting doses and inter-individual variation in response. Historically, and anecdotally, pubertal induction using oral ethinyloestradiol is effective but outcome data are scarce and suggest suboptimal outcomes in some cases. However, it is likely that the choice of oestrogen matters little at the start of pubertal induction and it is the low dosage which is of primary importance.

Ultimately, the most important requirement is that girls are treated with oestrogen in a timely manner and that this is continued through to natural menopausal age. It is well known that oestradiol deficiency causes cancellous bone loss, endothelial dysfunction, reduced insulin production, abnormal lipid patterns, increased central adiposity and early atheroma [4]. 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 [41]. Thus, the first priority is that girls receive treatment with oestrogen, either natural oestrogen or oral synthetic oestrogen. However, girls who are at risk of cardiovascular disease or with adverse metabolic profiles should be encouraged to pursue oral or transdermal natural oestrogen as their preferred option.

We are presenting three suggested regimens for pubertal induction in girls. Pubertal induction should be individualised with patient choice in mind, therefore taking the girls' views into consideration as well as parameters such as height and co-

morbidities. The optimal oestrogen treatment comprising route, drug, dose and dosing tempo have to be determined for each girl.

## IV Proposed Regimens For Pubertal Induction

It is generally agreed that starting doses for pubertal induction should be about 10% of adult replacement doses.

### a. Transdermal 17β-oestradiol

The published regimens for pubertal induction using transdermal 17β-oestradiol [2] [4] [5] were considered to be too difficult to implement in many centres in the UK. Their use could not be justified in view of the lack of evidence for their efficacy and concerns regarding errors arising in the case of widespread use.

In view of the lack of a good evidence base, a pragmatic approach to this regimen has been taken ensuring the use of low doses of oestradiol, particularly in early puberty [34], (personal communication Dr T Randell).

Regimen using 25mcg 17β-oestradiol matrix patch

Matrix patches are self-adhesive and release approximately 25mcg oestradiol /24 hours. Since the oestradiol is evenly distributed throughout the patch, the patches may be cut to provide the required dose of oestradiol. Practically, patches may be cut easily into ½ or ¼ but smaller, or more complex, divisions are prone to inaccuracies. The smaller fractions of patches may require the use of Mefix® tape or Opsite to ensure good adhesion to the skin. 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. The patches should not be applied above the waist, particularly avoiding the breast area.

| | |
|---|---|
| 25mcg patch | ¼ patch for 3-4 days, no patch 3-4 days for 6 months |
| 25mcg patch | ¼ patch all week (changing every 3-4 days) for 6 months |
| 25mcg patch | ½ patch for 3-4 days, ¼ patch for 3-4 days for 6 months |
| 25mcg patch | ½ patch all week (changing every 3-4 days) for 6 months |
| 25mcg patch | 1 patch all week (changing every 3-4 days) for 6 months |

Progress to adult oestrogen / progestogen replacement therapy as per section (IV e)

**A transdermal oestradiol dose of 12.5mcg/24 hours (½ x 25 mcg patch) gives an average serum oestradiol level of 40-50pmol/L.** Serum oestradiol levels below this are thought to accelerate growth with less effect on bone maturation [4].

## b. Oral 17β oestradiol

The following published regimen has been included following further correspondence with M Zacharin. The regimen has a faster tempo than the regimen for transdermal oestradiol described above. 17β-oestradiol is only available in 1mg tablets in the UK (roughly equivalent to 25mcg transdermal patch or 10mcg ethinyloestradiol) and the lack of smaller available doses may prove difficult for patient administration. There is very little experience with its use in the UK. and limited published guidance [11, 34]. Nevertheless, this regimen is widely used throughout Australia with observed good outcomes. However, review of the current literature suggests poorer outcomes compared with transdermal oestradiol [5, 24] and comparisons between oral 17β-oestradiol and ethinyloestradiol are very scanty.

Regimen using 1mg oestradiol valerate tablets

Oestradiol valerate 0.5mgs (½ tablet) alternate days for 12 months

Oestradiol valerate 0.5mgs (½ tablet) daily for 6 months

Oestradiol valerate 0.5mgs (½ tablet) and 1mg (1 tablet) on alternate days for 6 months

Oestradiol valerate 1mgs daily for 6 months

Progress to adult oestrogen / progestogen replacement therapy as per section (IV e)

Decisions on the timing of increases in dose depend on the presence of good breast development, concomitant treatment with human growth hormone and linear growth rate.

## c. Oral Ethinyloestradiol

Regimen using 2µg ethinyloestradiol tablets

The regimen derived from the proposed regimen for the UK Turner Study II produced by the consensus views of the co-investigators followed a slow tempo induction regimen over 3 years designed to optimise linear growth, particularly in the early stages of puberty. To rationalise and standardise induction regimens to 2.5 years, the following regimen is proposed alongside timings from the UK Turner Study II in brackets.

Ethinyloestradiol 2µg per day for 6 months (12 months)
Ethinyloestradiol 4µg per day for 6 months (12 months)
Ethinyloestradiol 6µg per day for 6 months (4 months)
Ethinyloestradiol 8µg per day for 6 months ( 4 months)
Ethinyloestradiol 10µg per day for 6 months (4 months)
Progress to adult oestrogen / progestogen replacement therapy as per section (IV e)

Regimen using 10µg ethinyloestradiol tablets

*Currently the availability of 2*µg *Ethinyloestradiol tablets is limited due to manufacturing availability. Therefore an alternative dosing regimen using 10mcg tablets may be used which takes into account the practicalities of cutting tablets, as these are not water soluble.*

| | |
|---|---|
| Ethinyloestradiol | 5µg (half 10 µg tablet) alternate days for 12 months (equivalent dose 2.5 µg daily) |
| Ethinyloestradiol | 5µg per day for 6 months |
| Ethinyloestradiol | 5µg and 10 µg alternate days for 6 months (equivalent dose 7.5 µg daily) |
| Ethinyloestradiol | 10µg per day for 6 months |

Progress to adult oestrogen / progestogen replacement therapy as per section (IV e)

## d. Monitoring of progress for all pubertal induction regimens

To ensure safety and efficacy of the suggested approaches, the following clinical data should be collected:

Prepubertal growth velocity and BP before treatment with oestrogen commences, together with a baseline pelvic USS to look at uterine dimensions and shape.

Progress through puberty should be monitored carefully recording height velocity, pubertal staging and BP every 6 months.

Bone age should be monitored annually.

Pelvic USS should be carried out once the final supplementation stage has been reached.

Bone mineral density should be measured once the final supplementation stage has been reached for a minimum of 1 year. Individuals with short stature have falsely low BMD readings on DXA and thus size-corrections need to be applied (such as lumbar spine BMAD, or total body BMD adjusted for height). Only in case of low size-corrected BMD or incompliance, should the DXA scan be repeated in 3-5 years.

## e. Progression to adult oestrogen / progestogen replacement therapy

A progestogen will be introduced for all patients for 12 days every 1-3 calendar months at breakthrough bleeding or after 3 years of treatment with oestradiol. The preferred progestogen is utrogestan 200mg once daily. This is a natural micronized progesterone which provides good cycle control and is the least androgenic. Alternatively, medroxyprogesterone 5mg daily is readily available and may be used. Norethisterone 5mg once daily may be used but is more androgenic than the other preparations and is linked to a higher incidence of dysmenorrhoea.

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

### Transdermal 17β-oestradiol

Transdermal 17β-oestradiol may be continued as a matrix patch, or an oestrogen gel (e.g. Sandrena®) may be preferred. Serum oestradiol levels may be monitored, aiming for an average of 350pmols/L. The dose of oestradiol may be adjusted in the light of the serum levels and the young woman’s feeling of wellbeing. Adult doses of transdermal oestradiol via patch vary between 50-100mcg/24 hours and adult doses of gel vary 0.5-1mg oestradiol daily.

### Oral 17β-oestradiol

Some young women may prefer an oral “HRT” preparation such as Elleste Duet. 1mg oral 17β-oestradiol is approximately equal to 10mcg ethinyloestradiol or 25mcg transdermal 17β-oestradiol patch. There are a number of different proprietary preparations which provide 1-2mg oral 17β-oestradiol daily according to requirement.

### 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 [42].

The COCP is generally cheap, readily available and acceptable socially in younger women. The contained oestrogen is usually ethinyloestradiol 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 avoid frequent “pill-free” weeks. This has the additional benefit of reducing the frequency of withdrawal bleeds.

### Choice of Progestogen

Many preparations are produced in user-friendly packs with tablets/patches containing oestrogen alone, followed by tablets/patches containing both oestrogen & progestogen combined (e.g. Elleste Duet® (oral), Evorel Sequi® (patch). Many oral “HRT” preparations contain norethisterone as the progestogen but in low doses of 0.5-1.0mg. Similarly the dose of medroxyprogesterone 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, it should be noted that women with any residual ovarian function may experience troublesome breakthrough bleeding on these preparations.

Progestogen may also be provided using a levonorgestrel-releasing intrauterine device such as the Mirena® coil. It is important to ensure that the uterus is of adult

dimensions by ultrasound before use and girls who are not sexually active may require a brief general anaesthetic for insertion.

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

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.

### f. The Use of Serum Oestradiol levels to Monitor Therapy

Girls and young women taking natural 17β-oestradiol for pubertal induction may have serum oestradiol levels measured to monitor therapy. Ethinyloestradiol cannot be assayed in serum.

During the first 12-18 months of pubertal induction, doses of oestradiol are low, aiming to mimic the low oestradiol levels found in normal girls going through early spontaneous puberty. Ideally, serum oestradiol levels should be maintained <50pmols/L during the first 18-24 months of pubertal induction to accelerate linear growth without rapid advance in bone maturation [4]. However, serum oestradiol levels <60pmols/L are not measured by most clinical laboratory methods. If the measurement of serum oestradiol levels is considered important e.g. in a girl who seems to be making either too slow or too rapid progress through puberty, an ultra-sensitive oestradiol assay is available in a few UK centres. In South Manchester, the assay is based on liquid chromatography tandem mass spectrometry with a limit of detection of 8pmols/L. Inter-assay coefficients of variation (CVs) for serum quality controls (QCs) are 3.4, 5.0 and 4.2% at concentrations of 352, 615, and 1184 pmols/L and intra-assay CVs 3.6, 4.1, and 2.4% at the same concentrations [43].

In young adult women standard laboratory oestradiol assays may be used to monitor serum oestradiol levels. Taboada et al., provided a target17β-oestradiol level of 350pmol/l. This was derived from healthy menstruating adult controls using integrated mean levels over the natural cycle and provides a useful guide for replacement therapy [6]

## Table of suggested oestrogen replacement regimens:

| Timing from start of induction months | 25mcg 17β-oestradiol matrix patch (e.g. Evorel® 25)** | 17 β-oestradiol (Oestradiol valerate 1mg tablets) | EE<br><br>2 mcg tablets | EE<br><br>10mcg tablets |
|---|---|---|---|---|
| **0** | ¼ patch for 3-4 days, no patch 3-4 days | 0.5 (1/2 tablet) alternate days | 2mcg daily | 5µg (1/2 tablet) alternate days |
| **6** | ¼ patch all week (changing every 3-4 days) | " | 4 mcg daily | " |
| **12** | ½ patch for 3-4 days, ¼ patch for 3-4 days | 0.5 (1/2 tablet) daily | 6mcg daily | 5µg (1/2 tablet) daily |
| **18** | ½ patch all week (changing every 3-4 days) | 0.5mg and 1mg alternate days | 8mcg daily | 5mcg and 10mcg alternate days |
| **24*** | 1 patch all week (changing every 3-4 days) | 1mg (1 tablet) daily | 10mcg daily | 10mcg daily |
| **30*** | Adult COC or HRT | Adult COC or HRT | Adult COC or HRT | Adult COC or HRT |

EE – Ethinyloestradiol

* 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. (see section IVe.)

** 50mcg 17β-oestradiol matrix patches (e.g. Evorel® 50) can also be used but cut to half the size of the 25mcg patches

## V 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 ethinylestradiol.

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.
- Transdermal patches may be less acceptable to girls undergoing pubertal induction, particularly if the patch becomes visible.
- There is some suggestion that there is inter-individual variation in response to oral 17β-oestradiol tablets and transdermal patches.
- There is very little published data about oral 17β-oestradiol regimens for pubertal induction.

Pros for oral ethinyloestradiol

- Oral ethinyloestradiol has been used extensively for pubertal induction over the last few decades and produces reliable outcomes (particularly in the UK).
- It is 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.

## VI References


1. Gault, E.J. and M.D.C. Donaldson, *Oestrogen replacement in Turner syndrome: current prescribing practice in the UK.* Clinical endocrinology, 2009. **71**(5): p. 753-5.
2. Ankarberg-Lindgren, C., et al., *Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls.* The Journal of clinical endocrinology and metabolism, 2001. **86**(7): p. 3039-44.
3. Ankarberg-Lindgren, C., B. Kristrom, and E. Norjavaara, *Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study.* Hormone research in padiatrics, 2014. **81**(4): p. 239-44.
4. Davenport, M.L., *Approach to the patient with Turner syndrome.* The Journal of clinical endocrinology and metabolism, 2010. **95**(4): p. 1487-95.
5. Nabhan, Z.M., et al., *Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study.* The Journal of clinical endocrinology and metabolism, 2009. **94**(6): p. 2009-14.
6. Taboada, M., et al., *Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome.* The Journal of clinical endocrinology and metabolism, 2011. **96**(11): p. 3502-10.
7. Illig, R., et al., *A physiological mode of puberty induction in hypogonadal girls by low dose transdermal 17 beta-oestradiol.* European journal of pediatrics, 1990. **150**(2): p. 86-91.
8. Bakalov, V.K., et al., *Uterine development in Turner syndrome.* The Journal of pediatrics, 2007. **151**(5): p. 528-31, 531.e1.
9. Piippo, S., et al., *Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome.* The Journal of clinical endocrinology and metabolism, 2004. **89**(7): p. 3241-7.
10. Critchley, H.O., C.H. Buckley, and D.C. Anderson, *Experience with a 'physiological' steroid replacement regimen for the establishment of a receptive endometrium in women with premature ovarian failure.* British journal of obstetrics and gynaecology, 1990. **97**(9): p. 804-10.
11. Bannink, E.M.N., et al., *Puberty induction in Turner syndrome: results of oestrogen treatment on development of secondary sexual characteristics, uterine dimensions and serum hormone levels.* Clinical endocrinology, 2009. **70**(2): p. 265-73.
12. Snajderova, M., et al., *The uterine length in women with Turner syndrome reflects the postmenarcheal daily estrogen dose.* Hormone research, 2003. **60**(4): p. 198-204.
13. McDonnell, C.M., L. Coleman, and M.R. Zacharin, *A 3-year prospective study to assess uterine growth in girls with Turner's syndrome by pelvic ultrasound.* Clinical endocrinology, 2003. **58**(4): p. 446-50.
14. Crofton, P.M., et al., *Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover.* Clinical endocrinology, 2010. **73**(6): p. 707-14.
15. Phelan, N., et al., *Quantification of the adverse effect of ethinylestradiol containing oral contraceptive pills when used in conjunction with growth hormone replacement in routine practice.* Clinical Endocrinology, 2012. **76**(5): p. 729-33.
16. Doerr HG, B.M., Hauffa BP, Mehls O, Partsch C-J, Said E, Sander S, Schwarz H-P, Stahnke N, Steinkamp H & Ranke MB, *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.* Human Reproduction, 2005. **20**(5): p. 1418-1421.
17. Quigley, C.A., et al., *Effects of low-dose estrogen replacement during childhood on pubertal development and gonadotropin concentrations in patients with Turner syndrome: results of a*

*randomized, double-blind, placebo-controlled clinical trial.* The Journal of clinical endocrinology and metabolism, 2014. **99**(9): p. E1754-64.
18. Paterson, W.F., A.S. Hollman, and M.D.C. Donaldson, *Poor uterine development in Turner syndrome with oral oestrogen therapy.* Clinical endocrinology, 2002. **56**(3): p. 359-65.
19. Ross, J.L., et al., *Growth hormone plus childhood low-dose estrogen in Turner's syndrome.* The New England journal of medicine, 2011. **364**(13): p. 1230-42.
20. Hogler W, B.J., Moore B, Garnett S, Lu PW, Cowell CT, *Importance of estrogen on bone health in Turner syndrome: a cross-sectional and longitudinal study using dual-energy X-ray absorptiometry.* Journal of Clinical Endocrinology & Metabolism, 2004. **89**(1): p. 193-9.
21. Soucek O, L.J., Snajderova M, Kolouskova S, Rocek M, Hlavka Z, Cinek O, RittwegerJ, Sumnik Z., *Bone geometry and volumetric bone mineral density in girls with Turner syndrome of different pubertal stages.* Clinical Endocrinology, 2011. **74**(4): p. 445-52.
22. Guttmann, H., et al., *Choosing an oestrogen replacement therapy in young adult women with Turner syndrome.* Clinical endocrinology, 2001. **54**(2): p. 159-64.
23. Norjavaara, E., C. Ankarberg, and K. Albertsson-Wikland, *Diurnal rhythm of 17 beta-estradiol secretion throughout pubertal development in healthy girls: evaluation by a sensitive radioimmunoassay.* The Journal of clinical endocrinology and metabolism, 1996. **81**(11): p. 4095-102.
24. Shah, S., et al., *A randomized trial of transdermal and oral estrogen therapy in adolescent girls with hypogonadism.* International journal of pediatric endocrinology, 2014. **2014**(1): p. 12.
25. Langrish, J.P., et al., *Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure.* Hypertension, 2009. **53**(5): p. 805-11.
26. Stegeman, B.H., et al., *Effect of ethinylestradiol dose and progestagen in combined oral contraceptives on plasma sex hormone-binding globulin levels in premenopausal women.* Journal of Thrombosis & Haemostasis, 2013. **11**(1): p. 203-5.
27. Piltonen, T., 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.* Human Reproduction, 2012. **27**(10): p. 3046-56.
28. Torres-Santiago, L., et al., *Metabolic effects of oral versus transdermal 17beta-estradiol (Eâ,,): a randomized clinical trial in girls with Turner syndrome.* The Journal of clinical endocrinology and metabolism, 2013. **98**(7): p. 2716-24.
29. Davies, M.C. and B. Cartwright, *What is the best management strategy for a 20-year-old woman with premature ovarian failure?* Clinical endocrinology, 2012. **77**(2): p. 182-6.
30. Chetkowski, R.J., et al., *Biologic effects of transdermal estradiol.* The New England journal of medicine, 1986. **314**(25): p. 1615-20.
31. Isotton, A.L., 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.* European journal of endocrinology / European Federation of Endocrine Societies, 2012. **166**(2): p. 207-13.
32. Powers, M.S., et al., *Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta-estradiol: comparison with conventional oral estrogens used for hormone replacement.* American journal of obstetrics and gynecology, 1985. **152**(8): p. 1099-106.
33. Labarta, J.I., et al., *Individualised vs fixed dose of oral 17beta-oestradiol for induction of puberty in girls with Turner syndrome: an open-randomised parallel trial.* European journal of endocrinology / European Federation of Endocrine Societies, 2012. **167**(4): p. 523-9.
34. Zacharin, M., *Pubertal induction in hypogonadism: Current approaches including use of gonadotrophins.* Best practice & research Clinical endocrinology & metabolism, 2015. **29**(3): p. 367-83.
35. Hindmarsh, P.C., *How do you initiate oestrogen therapy in a girl who has not undergone puberty?* Clinical endocrinology, 2009. **71**(1): p. 7-10.

36. Delemarre, E.M., B. Felius, and H.A. Delemarre-van de Waal, *Inducing puberty.* European journal of endocrinology / European Federation of Endocrine Societies, 2008. **159 Suppl 1**: p. S9-15.
37. Zacharin, M., *Disorders of ovarian function in childhood and adolescence: evolving needsof the growing child. An endocrine perspective.* British journal of obstetrics and gynaecology, 2010. **117**: p. 156-162.
38. Bergendal, A., et al., *Risk factors for venous thromboembolism in pre-and postmenopausal women.* Thrombosis Research, 2012. **130**(4): p. 596-601.
39. Schoemaker, M.J., et al., *Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study.* The Lancet Oncology, 2008. **9**(3): p. 239-46.
40. Mulder, R.L., 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 Oncology, 2013. **14**: p. e621-29.
41. Conway, G.S., M. Davies, and A. Merry, *Treatment of Turner's syndrome.* Lancet (London, England), 1996. **348**(9041): p. 1590-1.
42. Faculty of Sexual & Reproductive Healthcare of the Royal college of Obstetricians & Gynaecologists, *UK Medical Eligibility Criteria for Contraceptive Use*. 2010.
43. Owen LJ, F.C.a.K.B., *A rapid direct assay for the routine measurement of oestradiol and oestrone by liquid chromatography tandem mass spectrometry* Annals of Clinical Biochemistry, 2014. **51** (3):p. 360-367.

## VII Addendum

Table of different products to show relative costs (at time of publication April 2016)

| Type of Oestrogen | Proprietary Example | Quantity | Pack size | Cost per pack |
|---|---|---|---|---|
| Oral Ethinyloestradiol | Ethinyloestradiol | 2mcg<br>10mcg | 100 tablets<br>21 tablets | £242<br>£200 |
| Oral 17β-oestradiol (as valerate) | Elleste Solo | 1mg<br>2mg | 3 x 28 tablets<br>3 x 28 tablets | £5.06<br>£5.06 |
| Transdermal 17β-oestradiol | Evorel<br><br><br><br>Oestragel | 25mcg<br>50 mcg<br>75mcg<br>100 | 8 patches<br>8 patches<br>8 patches<br>8 patches<br>64 dose pump pack | £3.42<br>£3.88<br>£4.12<br>£4.28<br>£4.80 |

| Type of Progestogen | Proprietary Example | Quantity | Pack size | Cost per pack |
|---|---|---|---|---|
| Oral Progesterone | Utrogestan (contains arachis oil) | 100mg | 30 capsules | £5.13 |
| Oral Medroxyprogesterone | Climanor | 5mg | 28 tablets | £3.27 |
| Oral Norethisterone | Primolut N | 5mg | 30 tablets | £2.26 |

## VIII Acknowledgements

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