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 2 mcg tablets	EE 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

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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 10mcg	100 tablets 21 tablets	£242 £200
Oral 17β-oestradiol (as valerate)	Elleste Solo	1mg 2mg	3 x 28 tablets 3 x 28 tablets	£5.06 £5.06
Transdermal 17β-oestradiol	Evorel Oestragel	25mcg 50 mcg 75mcg 100	8 patches 8 patches 8 patches 8 patches 64 dose pump pack	£3.42 £3.88 £4.12 £4.28 £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

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