

Hormone supplementation for pubertal induction in girls

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Archives of
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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 17 β -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 17 β -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 17 β -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 17 β -oestradiol and oral ethinyloestradiol.

1
2
3 Pubertal induction aims to achieve normal tempo and magnitude of breast and
4
5 uterine development and adolescent growth spurt by mimicking the natural pubertal
6
7 process. These outcomes are achieved with low starting doses of oestrogen which
8
9 are then gradually increased, whilst monitoring the clinical response in linear growth
10
11 and breast staging. High dose oestrogen early in puberty or rapid dose escalation
12
13 may result in reduced final height and poor breast development, such as prominent
14
15 nipple development with poor supporting breast tissue. There are also concerns that
16
17 unphysiological supplementation may adversely affect uterine development and
18
19 bone mass accrual.[3]
20
21

22
23 Girls are known to prefer progress in tandem with their peers. Therefore, the
24
25 recommended age for commencing pubertal induction is around 11-12 years,
26
27 although some girls may actually present much later.
28
29

30
31 The aims of pubertal induction are to:-
32

- 33
34 • Allow the natural development of secondary sexual characteristics
35
36 (particularly breast shape and size).
- 37
38 • Allow normal uterine growth to an adult size and shape.
- 39
40 • Achieve a good adolescent growth spurt.
- 41
42 • Achieve normal peak bone mass.
- 43
44 • Support psychological maturation and adjustment.
45
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51 **LITERATURE REVIEW**

52
53
54 There is a real paucity of carefully constructed, randomised controlled clinical trials in
55
56 girls undergoing induction of puberty. The evidence base is derived mainly from
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1
2
3 expert experience, a small number of observational studies and very few controlled
4
5 trials on small study populations. In addition, studies of treatment acceptability and
6
7 patient adherence are lacking.
8
9

10 11 12 **Transdermal/Oral 17 β -oestradiol for Induction of Puberty**

13
14
15 17 β -oestradiol is the most physiological form of oestrogen, being identical to ovarian
16
17 secreted oestrogen and measurable in serum. Whilst oral 17 β -oestradiol is
18
19 metabolized in the liver to the weaker oestrogen oestrone, transdermal 17 β -
20
21 oestradiol does not undergo this first-pass effect. The available evidence on the use
22
23 of 17 β -oestradiol is sparse on all clinical outcomes mentioned above.
24
25

26 27 28 Transdermal 17 β -oestradiol

29
30 Three regimens using transdermal 17 β -oestradiol were reviewed. In a carefully
31
32 monitored observational study, Ankarberg-Lindgren et al., used a low dose
33
34 transdermal 17 β -oestradiol regimen in 15 girls with primary ovarian insufficiency
35
36 (POI) which resulted in pubertal development to breast stage 2-3 (B2-3) over a
37
38 period of 3.5-29 months (median 10 months).[4] However, this dosing regimen was
39
40 based on body weight with complicated cutting of patches into small fractions and
41
42 did not extend beyond early to mid-puberty. Davenport provided a regimen for
43
44 pubertal induction in girls with Turner syndrome basing transdermal 17 β -oestradiol
45
46 dose on body weight in early puberty, and adjusting patch size to target serum
47
48 oestradiol levels.[5] Nabhan et al. used much higher doses of transdermal 17 β -
49
50 oestradiol starting with 25 μ g/24hrs.[6]
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1
2
3 There is very limited but encouraging evidence on breast development [7], uterine
4 growth [8, 9] and bone accrual [10] in females treated with transdermal 17 β -
5 oestradiol. Because of its mode of administration, transdermal 17 β -oestradiol does
6 not lower IGF-1 levels since there is no effect on hepatic metabolism.[11] Therefore,
7 it might enhance linear growth although this has not been studied to date.[8]
8
9
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14 15 16 17 18 Oral 17 β -oestradiol

19
20 Four regimens using oral 17 β -oestradiol for pubertal induction were reviewed.
21 Zacharin used a starting dose of 0.5mg 17 β -oestradiol every second day, increasing
22 doses over 2 years to an adult dose of 2mgs daily.[12] Delemarre et al.[13] and
23 Bannink et al.[14] based 17 β -oestradiol dose on body weight, starting with
24 5 μ g/kg/day and increasing to an adult dose over 2 and 3 years respectively. Labarta
25 et al. used 0.2mg 17 β -oestradiol daily for one year, followed by 0.5mgs daily for the
26 second year.[15]
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36 In terms of clinical outcomes, Bannink et al. treated 56 girls with Turner syndrome
37 with incremental oral 17 β -oestradiol and described normal breast development up to
38 B4-5 in 49 girls (87%).[14] Labarta et al. treated 48 girls with Turner syndrome over 2
39 years using individualised or fixed dose 17 β -oestradiol and described breast
40 development to B4 in 42% and 65% of girls respectively.[15] The results from studies
41 looking at uterine growth are variable.[14, 16, 17] Torres-Santiago et al. found
42 significant but similar improvements in whole-body and lumbar BMD Z-scores over
43 12 months in 40 girls with Turner syndrome randomised to either oral or transdermal
44 17 β -oestradiol.[18]
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1
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3 Dose titration against serum oestradiol levels
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6 An ultrasensitive assay may be used to monitor serum 17β -oestradiol concentrations
7
8 in early puberty for both transdermal and oral 17β -oestradiol induction regimens.
9

10 These results may assist in adjusting doses of oestradiol aiming for serum
11
12 concentrations in the early pubertal range (10-40pmols/L).[4] Ankarberg-Lindgren et
13
14 al. showed that standard doses of transdermal oestradiol based on body weight
15
16 resulted in considerable inter-individual variation in serum 17β -oestradiol
17
18 concentrations highlighting the clinical value of using serum levels to guide dosing
19
20 regimens.[19] Conversely, the conclusion from Bannink's low-dose oral 17β -
21
22 oestradiol study was that serum oestradiol concentrations do not provide additional
23
24 information on the progression through puberty.[14] For those girls completing
25
26 puberty, a pharmacokinetic and pharmacodynamic study of oral and
27
28 transdermal 17β -oestradiol in girls with Turner syndrome suggested an adult target
29
30 17β -oestradiol concentration of 350pmol/l, as derived from healthy menstruating
31
32 adult women using integrated mean levels over the natural cycle.[20]
33
34
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40 **Oral Ethinyloestradiol for Induction of Puberty**

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42
43 Three published regimens for pubertal induction using ethinyloestradiol were
44
45 reviewed.[13, 21, 22] These regimens share a gradual increase in ethinyloestradiol
46
47 dose, either from a starting dose of $2\mu\text{g}$ daily [22] or $0.1\mu\text{g}/\text{kg}/\text{d}$ [13, 21] followed by
48
49 the addition of a progestogen after 2-2.5 years of unopposed oestrogen.
50

51
52 Ethinyloestradiol is synthetic, cannot be measured in serum, and undergoes first-
53
54 pass metabolism in the liver. Similar to 17β -oestradiol, published data regarding the
55
56 clinical efficacy of oral ethinyloestradiol in pubertal induction are very limited.
57
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1
2
3 Suboptimal breast development is reported in girls treated with ethinyloestradiol and
4 oestradiol valerate.[23, 24] However, it is unclear whether this is secondary to
5
6
7 problems with the formulation, dose effect, rate of dose escalation or timing of start
8
9
10 of therapy.[23] One study of 38 girls treated with incremental oral ethinyloestradiol
11
12 showed that only 50% developed mature, heart-shaped uterine configurations.[24]
13
14 Similarly, another study suggested that replacement therapy with ethinyloestradiol
15
16 gave rise to poor uterine growth and development.[3]
17
18

19
20 Few studies assessed the effect of ethinyloestradiol on bone mass accrual and there
21
22 are significant pitfalls in the interpretation of dual energy X-ray absorptiometry results
23
24 of children and adults with short stature such as in Turner syndrome.[25] A
25
26 randomised crossover trial in 18 young women with POI showed no significant
27
28 change in lumbar spine BMD z-score following ethinyloestradiol treatment, raising
29
30 concerns that this agent may not be effective in increasing bone mass.[10] Another
31
32 randomised crossover study in 17 young women with Turner Syndrome
33
34 demonstrated that ethinyloestradiol treatment was associated with high urinary
35
36 deoxypyridinoline cross-link concentrations, suggesting an unfavourable effect on
37
38 bone turnover.[26]
39
40

41
42 Oral ethinyloestradiol is associated with lower IGF-1 concentrations due to its first
43
44 pass hepatic effect although no studies have compared growth rates and final height
45
46 using different female hormone replacement strategies. A small synergistic effect on
47
48 final height was found between low dose childhood ethinyloestradiol and growth
49
50 hormone treatment in girls with Turner syndrome.[21]
51
52

53 54 55 56 **Introduction of Progestogens during Late Puberty** 57 58 59 60

1
2
3 Much of the literature considers the role of oestrogen in pubertal induction with little
4 discussion about the regimen, timing and choice of progestogens.
5
6

7
8 Progestogens are usually introduced after a suitable duration of unopposed
9 oestrogen (2-3 years) or if more than one episode of significant breakthrough
10 bleeding occurs. Progestogens are usually given in 12-14 day blocks, each inducing
11 withdrawal bleeding. The frequency of blocks may be adjusted according to the
12 patient's wishes, but at least every 2-3 months, which avoids endometrial
13 hypertrophy. Introducing a progestogen too soon, especially using one of the more
14 androgenic agents such as norethisterone, may potentially compromise uterine
15 growth and development.[3]
16
17

18
19 Options for treatment include oral Utrogestan (200mg once daily) or oral
20 Medroxyprogesterone acetate (5mg once daily). Utrogestan is a natural micronized
21 progesterone which can be given orally and gives good cycle control without
22 significant side effects. Medroxyprogesterone acetate is a synthetic derivative of
23 17 α -hydroxyprogesterone and is less androgenic than derivatives of 19-
24 nortestosterone such as norethisterone.[27]
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43 **Oestrogen and Progestogen Replacement Therapy in Adult Women**

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46 Adolescent girls undergoing pubertal induction require adult regimens at the end of
47 puberty. Similar to children and adolescents, no product is designed for long term
48 use in women with POI. Options include oral 17 β -oestradiol, transdermal 17 β -
49 oestradiol, the combined oral contraceptive pill (COCP) and equine conjugated
50 oestrogens (popular in the USA). Typical daily adult regimens for these preparations
51 are oral 17 β -oestradiol 2mg daily, transdermal 17 β -oestradiol 50-100 μ g patches
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1
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3 applied twice weekly and left in place until replaced, and COCP daily containing 20-
4
5 30µg of ethinyloestradiol.
6
7

8 In adult women, progestogen may be given cyclically or continuously depending on
9
10 whether women wish to experience withdrawal bleeds. Oral progestogens are
11
12 available either as single agents (e.g. Provera®) or in user-friendly combined packs
13
14 (e.g. Elleste-Duet®, Elleste-Duet Conti®) or as the COCP (e.g. Microgynon®,
15
16 Marvelon®). Combined transdermal patches with 17β-oestradiol and progestogen
17
18 are available, e.g. Evorel Sequi® & Evorel Conti®. However, breakthrough bleeding
19
20 may be more common in young women using transdermal progestogens.
21
22
23
24
25
26

27 Unfavourable cardiovascular risk of ethinyloestradiol/COCP

28
29
30 The COCP is cheap (free via the NHS in the UK) and readily available. However, if
31
32 taken as prescribed on a monthly cycle, women with POI lack oestrogen
33
34 supplementation 1 in 4 weeks. In addition, the COCP has an adverse cardiovascular
35
36 and metabolic profile. Specifically, the addition of the ethinyl side chain in
37
38 ethinyloestradiol induces renin substrate at a much greater rate than natural
39
40 products and increases the risk of hypertension, particularly in susceptible groups
41
42 such as women with Turner syndrome.[28] Use of the COCP is also linked with an
43
44 increased risk of venous thromboembolism.[29] Metabolic studies in adults suggest
45
46 that ethinyloestradiol treatment gives rise to increased SHBG, decreased IGF-1 and
47
48 increased insulin resistance.[11] In addition, C-reactive protein and other acute
49
50 phase reactants may increase which independently predict cardiovascular
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60 disease.[30]

1
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3 Studies comparing transdermal 17β -oestradiol with the COCP demonstrate reduced
4 blood pressure, better renal function and less activation of the renin-angiotensin
5 system in women using 17β -oestradiol.[31]
6
7

8
9
10 Women with POI are a heterogeneous group with different risk profiles. Women with
11 Turner syndrome seem to have a reduced risk of breast cancer (relative risk 0.3)
12 whereas women who have had whole body irradiation as conditioning for bone
13 marrow transplantation have an increased risk (relative risk 6.5).[32, 33] Both groups
14 of women are at greater risk of hypertension and Type 2 diabetes than their normal
15 peers and their choice of oestrogen replacement therapy needs to minimise these
16 risks. Women who have had cranial irradiation for brain tumours have an increased
17 risk of stroke and treatment with transdermal 17β -oestradiol is preferred.[34]
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32 **Summary of Literature Review**

33
34 In summary, pubertal induction using oral or transdermal 17β -oestradiol is well
35 described but there is some concern regarding appropriate starting doses and inter-
36 individual variation in response. The transdermal route of administration leads to
37 lower peak serum 17β -oestradiol concentrations, lower hepatic metabolism and
38 more stable steady state profiles compared with the oral route.[20] However,
39 transdermal products may be less acceptable to patients. Possibly, the choice of
40 oestrogen matters little at the start of pubertal induction where low dosage is of great
41 importance. While there is good evidence that puberty can be induced too quickly
42 leading to reduced final height, the question whether it can be induced too slowly
43 cannot be answered with confidence.[35] Review of the current literature suggests
44 that for long-term hormone replacement, oral/transdermal 17β -oestradiol needs to be
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1
2
3 favoured over preparations containing ethinyloestradiol, given their higher
4
5 cardiovascular risk.
6
7

8
9
10 Ultimately, the most important requirement is that girls with ovarian insufficiency are
11
12 treated with oestrogen in a timely manner and that treatment is continued through to
13
14 natural menopausal age. Oestradiol deficiency causes cancellous bone loss,
15
16 endothelial dysfunction, reduced insulin production, abnormal lipid patterns,
17
18 increased central adiposity and early atheroma.[5] Hence, it is concerning that at a
19
20 large UK adult Turner clinic, 24% of patients were not receiving oestrogen treatment
21
22 at all at their first clinic attendance.[36], highlighting the importance of treatment
23
24 acceptability, adherence and patient education.
25
26
27

28
29 Finally, there is very little information on specific dose response (breast and uterine
30
31 growth and shape, bone accrual, growth) to oral or transdermal 17 β -oestradiol and
32
33 oral ethinyloestradiol, and the bioequivalency of preparations. Estimated daily dose
34
35 equivalence from the current literature (depending on assays and clinical endpoints)
36
37 are: **50/100 μ g transdermal** (applied twice weekly until replaced) = **2mg oral 17 β -**
38
39 **oestradiol** (per day) = **20 μ g ethinyloestradiol** (per day).[5, 37]
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46 **PROPOSED REGIMENS FOR PUBERTAL INDUCTION**

47
48
49 Pubertal induction should be individualised taking the girl's and family's views into
50
51 consideration as well as parameters such as height, age, pubertal stage and co-
52
53 morbidities. The optimal oestrogen treatment comprising route, drug, and dose
54
55 increments should be determined for each girl. Amongst the paediatric endocrine
56
57 community, there is general agreement that oestrogen starting doses for pubertal
58
59
60

1
2
3 induction should be about 10% of adult replacement doses. Following extensive
4
5 literature review, consultation with external experts and the UK Turner Syndrome
6
7 support group, we present below optimised regimens for pubertal induction in girls
8
9 with ovarian insufficiency. All induction regimens will take girls into later pubertal
10
11 stages (Tanner 3-5) over 2.5 years, following which adult hormone replacement
12
13 options should be used.
14
15

16 17 18 19 20 **Transdermal 17 β -oestradiol**

21
22 The published regimens for pubertal induction using transdermal 17 β -oestradiol were
23
24 considered impractical to administer and implement.[4-6] Therefore, a pragmatic
25
26 approach to the transdermal regimen was taken, ensuring the use of low doses of
27
28 17 β -oestradiol, particularly in early puberty.[12] (personal communication with M
29
30 Zacharin and T Randell, 2016).
31
32

33 34 Regimen using 25 μ g 17 β -oestradiol matrix patch (**Table 1**)

35
36 Matrix patches are self-adhesive and release approximately 25 μ g 17 β -oestradiol /24
37
38 hours. Since the oestradiol is evenly distributed throughout the patch, the patches
39
40 can be cut to provide the required dose. Practically, patches are cut into $\frac{1}{2}$ or $\frac{1}{4}$ as
41
42 more complex divisions would be prone to inaccuracies and impracticable. Unused
43
44 patch fractions may be stored in their packaging in the fridge for up to one week. The
45
46 patch (or patch fraction) should be applied to clean dry skin over the buttocks or hips
47
48 using Opsite® (a transparent adhesive film) if necessary to ensure good adhesion.
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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

1
2
3 levels should be maintained <50pmols/L during the first 18-24 months of pubertal
4
5 induction to accelerate linear growth without rapidly advancing bone maturation.[5]
6
7 However, serum oestradiol levels <60pmols/L are not measurable by most clinical
8
9 laboratory methods. If a girl seems to be making either too slow or too rapid progress
10
11 through puberty, ultra-sensitive oestradiol assays should be employed. Such assays
12
13 are based on liquid chromatography tandem mass spectrometry with limits of
14
15 detection of 4-8pmols/L.[38]
16
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22 **Oral Ethinyloestradiol**

23
24 This regimen is derived from Hindmarsh.[22] (**Table 3**) Ethinyloestradiol is not easily
25
26 measured in serum.
27
28
29
30
31
32

33 **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

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44 Progress to **adult oestrogen / progestogen replacement therapy**
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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	Ethinylloestradiol 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 25 μ g/24h, oral 17β -oestradiol 1mg or oral ethinyloestradiol 10 μ g is reached and the girls are receiving a cyclical progestogen, there are further options for their longer term management as young women.

Transdermal / oral 17 β -oestradiol

Transdermal 17 β -oestradiol may be continued as a matrix patch or an oestrogen gel (e.g. Sandrena®). Adult doses of transdermal oestradiol via patch vary between 50-100 μ g/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 17 β -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 17 β -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]

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3 Women with any potential residual ovarian function in whom pregnancy is not
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5 desired should be counselled about the need for additional contraception if using
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7 these preparations.
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10 11 12 13 **Combined Oral Contraceptive Pill (COCP)** 14

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16 Advice on the use of the COCP for adult replacement therapy should be guided by a
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18 risk assessment as set out by the Faculty of Sexual & Reproductive Healthcare.[40]
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20 The contained oestrogen is usually ethinyloestradiol (e.g. Microgynon30®,
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22 Marvelon®) although 17β -oestradiol is used occasionally (e.g. Qlaira®). In order to
23
24 maximise oestrogen exposure, girls are advised to take at least 3 packs of pills
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26 “back-to-back” to reduce “oestrogen-free” weeks. This has the additional benefit of
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28 reducing the frequency of withdrawal bleeds. Preparations can also be taken
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30 continuously to avoid withdrawal bleeding although initially there may be some
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32 breakthrough bleeding until the endometrial lining is atrophied.
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36 The full scope of oestrogen/progestogen replacement for adult women is beyond the
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38 remit of this guideline. It is anticipated that young women with ovarian insufficiency
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40 will be reviewed in a Transition clinic alongside an adult Gynaecologist or an adult
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42 Endocrinologist and kept under review throughout adult life.
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46 47 48 49 **CONCLUSION AND RESEARCH NEEDS** 50

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52 The induction regimens proposed here are based on synthesis of the literature,
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54 expert views, consultation, pragmatism and practicability. The evidence suggests
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56 that transdermal 17β -oestradiol has the most favourable efficacy, safety and cost
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3 profile. Therefore, this BSPED working group recommends it as first choice for
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5 pubertal induction in girls.
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8 Nevertheless, how the essential clinical outcomes (breast and uterine size and
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10 shape, final height, bone mass, safety and acceptance) compare between regimens
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12 has not been well studied. The lack of randomised controlled studies on pubertal
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14 induction in girls needs to be addressed. It is anticipated that prospective collection
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16 of data from these proposed regimens will provide valuable information about their
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18 efficacy and acceptability.
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Pros and Cons of oral/transdermal 17 β -oestradiol versus oral ethinyloestradiol for pubertal induction in girls

Pros for oral / transdermal 17 β -oestradiol

- 17 β -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 17 β -oestradiol is effective at inducing puberty. Treatment using transdermal 17 β -oestradiol can be individualised and can mimic normal puberty closely.
- Oral 17 β -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 17 β -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 17 β -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 μ g) 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 17 β -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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