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Sex Steroid Treatment for Pubertal Induction and Replacement in the Adolescent Girl

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1. Introduction

Girls with hypogonadism require sex steroid replacement that allows for progression through puberty as in girls with normal gonadal function. Inevitably, many girls presenting with pubertal delay will require a shortened protocol of sex steroid replacement so that their development catches up with their peers. Historically, several forms of oestrogen and progesterone have been used for the induction of puberty with the choice being based mainly on local tradition.

The main issues for consideration include the timing of the initiation of oestrogen for girls with known oestrogen deficiency,[1] the duration of unopposed oestrogen to be achieved to mimic normal puberty, possible interference with other pubertal treatment such as growth hormone and the plan for maintenance treatment once adult dose has been achieved.

Sex steroids also have a place for use in eugonadal adolescents for contraception, for the control of menstrual bleeding complaints and to suppress androgen excess in the polycystic ovary syndrome (PCOS) but these topics are outwith the scope of this paper.

2. Normal pubertal development

The overall aim of induction of puberty in girls with hypogonadism is to achieve timely secondary sex characteristics including breast and uterine development. This leads to menses, generation of the pubertal growth spurt and finally, acquisition of peak bone mass which continues to approximately the age of 30.[2]

The first oestrogen effects to show will be breast budding which will have occurred in 50% of girls by the age of 11.3 years. Breast development continues to breast stage four (near full development with elevated areola) by the age of 13.3 in 50% of girls. The average age of menarche in the UK is 13.

With respect to bone development there are the competing effects of low–dose oestrogen which increases height velocity and higher dose oestrogen that results in closure of the epiphyseal growth plates. The majority of breast development therefore occurs over the two years prior to menarche. In treatment terms, this would be the equivalent of two years of unopposed oestrogen.

3. Definition of delayed puberty

Delayed puberty can be defined by the ages at which 95% of girls achieve breast stage 2 (clear elevation of the breast mound and enlargement of the areola as breast budding), which is 13 years of age. Menarche will have occurred in 95% of girls by age 14.5.[2–4] Therefore; girls with complete absence of breast development should be referred for full evaluation from the age of 13 and those with primary amenorrhoea, but normal breast development, by the age of 15. The latter presentation implies no deficiency of oestrogen and includes anatomical causes such as Rokitansky syndrome and also euoestrogenaemic causes of amenorrhoea such as PCOS. Late presentations are common.

A list of common conditions resulting in oestrogen deficiency in adolescents is shown in Table 1. Of the few trials in this area, the majority focus on either Turner syndrome, because it forms a relatively homogeneous population, or those receiving growth hormone because of the complex effects of oestrogen on growth.

4. Timing of the induction of puberty

The induction of puberty with exogenous oestrogen should aim to achieve the milestones of puberty in

Table 1. Common conditions requiring sex steroid replacement

Constitutional delay of puberty
Gonadal dysgenesis – 45X, 46XX, 46 XY
Premature ovarian insufficiency
Surgical hypogonadism
Hypopituitarism
Hypogonadotrophic hypogonadism
Hypothalamic amenorrhoea
Disorders of sexual development

a timely manner.[5] In young girls who are known to be oestrogen deficient, low–dose oestrogen administration could start at the age of 10.[6] In this situation a full 2–3 years of unopposed oestrogen could be achieved before progesterone is introduced to trigger the first withdrawal bleed at the age of 13.The administration of progesterone should always follow oestrogen by some months and so the combined oral contraceptive pill is never used for the initiation of puberty.

A more common situation is a girl presenting with delayed puberty in her teenage years where exposure to oestrogen will be at least four years late.[3,4,6] In this situation the starting dose and rate of increase in dosage of oestrogen will be individually tailored depending on the age of presentation and also of the concerns of the individual. It is important that each adolescent engages with the process and takes part in the decision making regarding dose adjustment in the interval up to menarche. However late a girl's presentation, it is usually possible to allow between 6–12 months of unopposed oestrogen before introducing progestogens.

It is commonly observed that the late administration of oestrogen can result in impaired breast development leading to the concept of an optimal window during which breast and uterine development can be best achieved. Early administration of progestogen may have an adverse effect on breast development. However, it has to be accepted that these concepts are theoretical and without a clear evidence base. Nevertheless the combined oral contraceptive should be avoided for the initiation of puberty at any age.

5. Induction of puberty regimens

The evidence base for the induction of female puberty with sex steroids is derived mainly from expert experience[2,3,6,7] with a small number of observational trials[7–11] and very few controlled trials with small study groups.[12,13] Randomised trials are particularly difficult in this area because of the heterogeneous population, endpoints that are difficult to quantify precisely and the long duration that is required. Some guidance can be obtained from studies of the administration of oestrogens in older populations with ovarian failure.[14–16]

Regimens often start at 12 years of age. This is based on studies of girls who are also receiving growth hormone, as early reports showed that exogenous oestrogen administered too early and at too high a dose results in diminished final height because of earlier closure of epiphyses. Administering oestrogen in this circumstance must be undertaken in conjunction with a paediatric endocrinologist. In the UK ethinylestradiol is commonly used, possibly because of perceived peer group acceptance but most recent papers favour the use of transdermal matrix patches. Congugated equine oestrogen is often used in the USA.[3,19] Oral oestradiol is a less convenient option because of difficulties in achieving low starting doses. There is increasing evidence that ethinylestradiol is inferior to transdermal oestradiol in terms of blood pressure and bone density[17,18] and thus transdermal oestradiol is currently the preparation of choice (Table 2).

Table 2. Published examples of induction of puberty regimens

Age	Ethinylestradiol[2,6]	Oestradiol[6]	Oestradiol[5]
		Oral	Patch
	mcg	mcg/kg	mcg/24hrs
8	2		
9	4		
10	6		
11	8		
12	10	5.0	3.1–6.25
13	15	7.5	6.25–12.5
14	20	10.0	12.5–18.8

Progestogen is introduced only after a suitable duration of unopposed oestrogen or if break through unscheduled bleeding occurs. Progestogen is usually given as part of a pre–packed cyclical regimen with oestradiol using one of the preparations formulated for post–menopausal women. Progestogens can also be prescribed separately if a particular one is favoured because of side effects. Northisterone, the most potent progestogen, may be considered excessive in this situation and fewer side effects may be experienced with medroxyprogesterone acetate or micronized progesterone prescribed for 12–14 days each cycle. It is also possible to administer the progestogen every 2–3 months to reduce the frequency of withdrawal bleeding. Progestogen cover can also be achieved using the oral contraceptive pill.

6. A summary of studies of oestrogen replacement in adolescents

The general theme that develops from the studies of oestrogen used in adolescents is that timely induction of puberty should probably begin with very low dose transdermal oestrogen at about the age of 10 years. In subjects who also require growth hormone treatment there is a tendency to delay the introduction of oestrogen to 12 years of age although earlier timing with sufficiently low doses of oestrogen is now thought to have no adverse effect on final height and should be considered.[20,21] For those who present late, shortened protocols are generally successful although available studies are too small to clearly identify the reasons for unsatisfactory pubertal outcomes such as breast hypoplasia. No good data on long term outcomes such as peak bone mass are available.

Combined oral contraceptive pills containing ethinylestradiol, being unphysiological in their formulation, do not provide optimal oestrogen replacement in young women and should only be used if contraception is required,[17,19,21] such as in girls with ovarian failure, hypothalamic amenorrhoea or hypogonadotrophic hypogonadism in whom a return of normal ovarian function is a possibility.

Adolescents with hypothalamic amenorrhoea caused by eating disorders and low body weight are at particular risk of low bone density as adipose tissue is a source of oestrone that supports bone development. As the return of menstruation can be delayed for some months even after regain of body weight, oestrogen replacement should be introduced as soon as this form of deficiency is recognised.

In summary, current opinion favours induction of puberty with transdermal oestradiol patches starting at a dose of 6.25 mcg in the younger age groups and 12.5 mcg in older age group. The timing of dose escalation should be individualised taking into account the potential for further growth potential. This treatment should only be initiated with input from a paediatric endocrinologist.

7. Research Topics

- Outcomes for endometrial and breast cancer, cardiovascular health and bone density for long–term users of oestrogen replacement
- Controlled trails comparing different oestrogen/progestin regimens

8. Opinion

For all girls presenting with primary amenorrhoea, it is mandatory to assess potential for growth with involvement of a paediatric endocrinologist before starting oestrogen. In adolescent girls with delayed puberty, the introduction of oestrogen should be initiated using fractions of a transdermal matrix oestradiol patch with the aim of achieving some months of unopposed oestrogen administration. The dose of oestrogen is then increased until breakthrough bleeding occurs or is expected, after which cyclical progestins are introduced.

In hypogonadal girls who are established on oestrogen replacement, regimens using transdermal oestradiol patches should be considered. Further studies are required to establish the role for this route of delivery with respect to cardiovascular and bone outcomes. The role of combined oral contraceptives is limited to those in whom the return of ovarian function is possible and who require contraception.

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