replacing oestrogens in the adolescent...

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Clinical Advisor, NICE women’s health guideline programme
Conflicts of Interest - none

- Co-chair ESHRE guideline, Premature Ovarian Insufficiency
- Member NICE guideline group, Menopause: diagnosis and management
- Founder member BRITsPAG
- Adolescent transition clinics (endocrine, metabolic, oncology) and service for POI
adolescence

‘the period of development from a child to an adult’

a time of transition

WHO age 10-19
young people <25
Presenting problem

- absent or arrested puberty - usually to paediatrician
- primary amenorrhoea – varying degrees of pubertal development – often presents to gynaecologist
- secondary amenorrhoea – usually gynaecologist

Oestrogen replacement is central to management
Underlying conditions

- ↑FSH & LH (primary hypogonadism)
  - POI
  - Turner Syndrome
  - Cancer treatment (chemo/radiotherapy)
  - Surgery eg ovarian torsion/gonadectomy
  - 46XY DSD (gonadal dysgenesis, CAIS)
Underlying conditions

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- ↓LH & FSH (secondary hypogonadism)
  - Weight loss, exercise
  - Hypopituitarism eg CNS tumour, radiotherapy
Underlying conditions

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- \( \text{n FSH} & \uparrow \text{LH} = \text{PCOS} \)
Puberty: normal progress

- Breast bud: 10.5 years
- Onset pubic hair: 11.0 years
- Peak height velocity: 11.4 years
- Menarche: 12.8 years
- Adult breast: 14.6 years
- Adult pubic hair: 13.7 years

Age in Years
Induction of puberty: principles

- puberty takes time
- development requires unopposed oestrogen
- monitor breast +/- uterine growth
- progesterone for menarche/cyclical bleeding
Induction of puberty: principles

- age 11-12 yrs onwards
  - slowly increase dose over 2-3 years
  - add progestogen at menarche

- common regimens:
  - oral EE in escalating dose (2, 4, 6, 10, 15, 20 mcg)
  - transdermal E2 (25mcg patch 1/4, 1/2, 1, 11/2..)
Induction of puberty: outcomes
aims of oestrogen replacement

- height
- secondary sexual characteristics
  - breasts
  - uterus - fertility potential
- psychology
  - relationships
  - sexuality
- bone strength
- cardiovascular protection
- cognition
Relationship between the timing of induction of puberty in TS and subsequent uterine volume

n = 32, r = -0.53, p = 0.002

Sakine Mohseni, unpublished
pregnancy and uterine volume (Turner syndrome egg recipients, n=42)

Vol cm³

0
10
20
30
40
50
60
70

not pregnant pregnant
timing of induction of puberty

- 475 patients with primary amenorrhoea attending Turner syndrome clinic at UCLH
- age of starting oestrogen: median 14 years (range 11-20 years). This correlated with:
  - hip T-score p=0.001
  - systolic BP p=0.015
  - liver enzymes, GGT p=0.006
  - HbA1C, p<0.001

Antoinette Pimblett
abstract Endo 2017
what is the best oestrogen replacement?
COCP vs HRT

- EE synthetic
- EE more potent
- available
- like peer-group
- contraceptive
- Pill-free week

- E2 physiological (natural)
- E2 safer for long-term use?
- stigma of HRT
- not contraceptive
- continuous oestrogen
COCP vs HRT [1]

Open-label randomized cross-over trial
12 months of physiological HRT vs COCP
- transdermal E2 100-150mcg + vaginal P 100mg bd 14/28 days
- oral EE 30mcg + NET 1.5mg for 21/28 days

POF of any cause
Recruited 42 women, 18 completed study.
Age median 25 (19-33) yrs

Langrish Hypertension 2009
Crofton Clin Endocrinol 2010
COCP vs HRT [1]

24-hour BP monitoring:
physiological regimen lowered BP by 7.3mmHg  \( p<0.0001 \)

DEXA lumbar spine:
physiological regime improved BMD z-score +0.17 vs +0.07

biochemistry:
physiological regimen increased bone formation markers & improved renal function
COCP vs HRT [2]
Liver function tests in Turner Syndrome

17 women with TS, sampled at end of 3-4 months off treatment, 6 months on HRT (CE+MPA), 6 months on COCP
Open bars: Alanine aminotransferase ** p<0.005, *** p<0.0005 vs pretreatment levels
Shaded bars: Asparate aminotransferase ** p<0.005, *** p<0.0005 vs other Rx
Filled bars: Gamma glutamine transferase a p<0.05, b p<0.005 vs other Rx

Guttman et al 2001
COCP vs HRT [3]

- Two-year open randomised trial comparing HRT with COCP, with non-randomised observation of women declining treatment, main outcome BMD
- 59 recruited, 36 completed trial

- Both HRT and OCP better than no treatment
- Results favoured HRT
  Lumbar spine $+0.05 \text{ g cm}^{-2}$ (95% CI 0.007-0.092, $p=0.25$)

Cartwright JCEM 2016
COCP vs HRT [4]

- Retrospective analysis of case records in POI clinic
- Women identified who only used COCP or only used HRT for at least 3 years; n=44
- Serial measurement (DEXA) of lumbar spine and femur

<table>
<thead>
<tr>
<th></th>
<th>OCP</th>
<th>HRT Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>BMD</td>
<td>-0.17% decrease per year</td>
<td>+0.99% increase per year</td>
</tr>
<tr>
<td></td>
<td>-0.18 at hip &amp; -0.16% at spine</td>
<td>+0.8% at hip &amp; +1.18% at spine</td>
</tr>
</tbody>
</table>

BMD increased significantly with oral HRT compared to COCP (P<0.01)

V Talaalikar, E Yasmin, M Davies, G Conway
University College London Hospitals, UK in preparation
what dose and route?

OCP EE 20, 30, 35 mcg
Oral HRT oestradiol 1-2mg
Transdermal HRT oestradiol 50 mcg

standard HRT doses may not be enough for young women but need dose-finding studies
transdermal advantages but less acceptable to patients
?100mcg patch with progesterone 200mg x 14/28
do I need periods?

- progestogen for endometrial protection
- cyclical or continuous therapy?

- special circumstances:
  spasticity, learning difficulties
  role of Mirena IUS, Tibolone
how do you monitor HRT?

feedback from patient

routine BP weight every year
+ advice on CVS / BMD protection

blood tests for oestrogen level are of little value

gynae exam not needed unless symptoms

BMD every 3-5 years
no evidence on value of ultrasound
Key points

- Induction of puberty has long-term consequences
- Transition to long-term adult care is crucial
- Current evidence favours HRT over COCP for bone density and BP
- However, patient preference and need for contraception should be taken into account
thank you
thank you

Caroline Brain
Vicky Grandage
Elaine Murphy

Gerry Conway
Vikram Talaulikar
Antoinette Pimblett
further reading

ESHRE guideline on POI

puberty:
Sabine De Muinck Keizer
HRT:
Femi Janss
Lisa Webber
## Induction of puberty

<table>
<thead>
<tr>
<th>age</th>
<th>age-specific suggestions</th>
<th>preparation, dose</th>
</tr>
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<tbody>
<tr>
<td>12 - 13 years</td>
<td>If no spontaneous development and FSH elevated, start low dose estrogens</td>
<td>17β-estradiol (E2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transdermal (TD): 6.25 µg/day E2 via patch</td>
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<td></td>
<td>Oral micronized E2: 5 µg/kg/day or 0.25 mg/day</td>
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<tr>
<td>12.5 - 15 years</td>
<td>Gradually increase E2 dose at 6-12 months interval over 2 - 3 years to adult dose</td>
<td>TD E2: 12.5, 25, 37.5, 50, 75, 100 µg/day. <strong>Adult dose</strong>: 100-200 µg/day</td>
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<tr>
<td></td>
<td></td>
<td>Oral E2: 5, 7.5, 10, 15 µg/kg/day. <strong>Adult dose</strong>: 2-4 mg/day</td>
</tr>
<tr>
<td>14 - 16 years</td>
<td>Begin cyclic progesterone after 2 years of estrogen with pelvic ultrasound, or when breakthrough bleeding occurs</td>
<td>Oral micronized progesterone 100-200 mg/day or dydrogesterone 5-10 mg/day during 12 – 14 days of the month</td>
</tr>
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Puberty Induction: Current Approach

<table>
<thead>
<tr>
<th>Year</th>
<th>Dosage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Y1</td>
<td>6.25μg/24hrs</td>
<td>¼ “25” patch</td>
</tr>
<tr>
<td>Y2</td>
<td>12.5μg/24hrs</td>
<td>½ “25” patch</td>
</tr>
<tr>
<td>Y3</td>
<td>18.75μg/24hrs</td>
<td>3/4 “25” patch for 6/12, 25μg/24hrs (“25” patch) for 6/12</td>
</tr>
<tr>
<td>Y4</td>
<td>60μg/24hrs</td>
<td>“50” patch</td>
</tr>
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- Oral EE2
  - Y1: 2 μg/daily
  - Y2: 4 μg/daily
  - Y3: 6 μg/daily for 6/12, 10 μg/daily for 6/12
  - Y4: 20 μg/daily
Sarah  age 17

- healthy childhood
- normal puberty
- menarche aged 13 ½
- second period 3 months later
- two more periods at 6 month intervals
Sarah  age 17

- healthy childhood
- normal puberty
- menarche aged 13 ½
- second period 3 months later
- two more periods at 6 month intervals

- normal weight & height
- breast and pubic hair fully developed
- FSH >100,  E2<40
- ultrasound very small ovaries, no follicles seen