Anne Trinh, Angelina Lim, Phillip Wong, Justin Brown, Janne Pitkin, Beverley Wollenhoven, Peter Ebeling, Peter Fuller, Frances Milat and Margaret Zacharin*

A pilot study proposing an algorithm for pubertal induction in cerebral palsy

https://doi.org/10.1515/jpem-2024-0013
Received January 6, 2024; accepted January 18, 2024;
published online February 20, 2024

Abstract

Objectives: To explore delayed puberty in cerebral palsy (CP) and to test the acceptability of an interventional puberty induction algorithm.

Methods: A two phase cohort study in children and adolescents diagnosed with CP who have delayed puberty. Phase 1: Retrospective review of clinical records and interviews with patients who have been treated with sex-steroids and Phase 2: Prospective interventional trial of pubertal induction with a proposed algorithm of transdermal testosterone (males) or oestrogen (females). Phase 1 examined experiences with sex-steroid treatment. Phase 2 collected data on height adjusted bone mineral density (BMAD), fractures, adverse effects, mobility and quality of life over two years during the induction.

Results: Phase 1, treatment was well tolerated in 11/20 treated with sex-steroids; phase 2, using the proposed induction algorithm, 7/10 treated reached Tanner stage 3 by nine months. One participant reached Tanner stage 5 in 24 months. Mean change in BMAD Z-scores was +0.27 % (SD 0.002) in those who could be scanned by dual-energy X-ray absorptiometry (DXA).

Conclusions: Delayed puberty may be diagnosed late. Treatment was beneficial and well tolerated, suggesting all patients with severe pubertal delay or arrest should be considered for sex hormone supplementation.

Keywords: cerebral; hypogonadism; puberty; disability; hormones

Introduction

Cerebral palsy is the most common disorder of movement seen in children, affecting 2–3.5/1,000 live births [1]. With improved life expectancy, there has been an increased focus on musculoskeletal morbidity in adults with CP. The prevalence of osteoporosis in a large North American cohort of adults with CP was 10 % in those aged 31–40 years, increasing to 25 % in those over 50 years of age [2]. Fracture prevalence was 38 % in a cohort of 45 young adults with CP, with over half of fractures occurring in adulthood [3]. Low bone mass leading to fractures can impair mobility and quality of life.

The abnormal bone phenotype in cerebral palsy commences in childhood, with less bone accrual due to reduced biomechanical forces exerted on bone, compounded variably by anticonvulsant use, inadequate nutrition, vitamin D deficiency and growth hormone deficiency [4–6]. The role of sex-steroids requires further exploration, with altered pubertal progression and hypogonadism described in CP [7, 8].

Delayed progression through puberty is reported in girls with CP, having late menarche despite entering puberty earlier [9]. Reported aetiologies of delayed puberty or hypogonadism in CP include a case series of hypopituitarism [10]. Both hyper- and hypogonadotrophic hypogonadism have been identified in young adults with CP [3].

Unequivocal evidence for the adverse effects of hypogonadism on bone health in this population is lacking. Studies of adults with CP have demonstrated an association between hypogonadism, lower lumbar spine bone mineral density (BMD) and reduced muscle mass [3]. Studies assessing bone age in CP are conflicting, showing both advanced [11] and delayed skeletal age, influenced by the degree of functional impairment and fat stores [12–14]. Importantly, no studies have examined tolerability of

***Corresponding author: Prof. Margaret Zacharin**, Royal Children's Hospital, 50 Flemington Rd, Parkville 3052, Melbourne, Australia, E-mail: margaret.zacharin@rch.org.au
Anne Trinh, Justin Brown, Beverley Wollenhoven and Peter Ebeling, Monash Health, Clayton, VIC, Australia; and Monash University, Melbourne, VIC, Australia
Angelina Lim, Murdoch Children's Research Institute, Parkville, VIC, Australia; and Monash University, Melbourne, VIC, Australia. https://orcid.org/0000-0002-8219-1191
Phillip Wong and Frances Milat, Hudson Institute of Medical Research, Clayton, VIC, Australia; and Monash University, Melbourne, VIC, Australia
Janne Pitkin, Murdoch Children's Research Institute, Parkville, VIC, Australia
Peter Fuller, Hudson Institute of Medical Research, Clayton, VIC, Australia

pubertal induction and/or sex-steroid replacement in this population specifically and its effect on bone health. Much of the literature in females with chronic neurological disabilities, including CP, focuses on contraception or menstrual suppression. In both sexes, concerns regarding mood, aggression or altered sexual behaviour may discourage treatment being sought [15]. Furthermore, there has been no proposal for a treatment algorithm for safe induction of puberty in CP.

In this study, we aimed to provide clinicians with data on delayed puberty in our cohort, treatments and their tolerability and effects on bone density. Subsequently, we tested a pubertal induction algorithm to guide future management in this cohort.

Methods

Study design

A two phase study conducted in patients with CP who have delayed puberty:

1) Retrospective review of clinical records and interviews with patients (or their carers) who have been treated with sex-steroids.
2) Prospective interventional trial of pubertal induction with a proposed algorithm in a cohort of CP patients (separate from phase 1).

Outcomes

Phase 1 outcomes include incidence of hypogonadism and delayed puberty in children with cerebral palsy, types of sex-steroid use and experience of those who were treated with sex-steroids. Phase 2 outcomes included tolerability of pubertal induction (measured by adverse events and progression to different tanner stages) and bone mineral density gain.

Participants

Phase 1: Participants were included if identified from either of the two tertiary paediatric hospital databases (up to 2018) as having CP and pubertal delay. Those treated with sex-steroids were invited to participate in a telephone interview about their experience.

Phase 2: Participants were recruited from outpatient clinics from January 2017 to December 2021 if they were diagnosed with CP (4 or 5 on the Gross Motor Function Classification System (GMFCS) [16] or level 2–3 if they had other complex needs such as multiple anticonvulsant use and were either pre-pubertal or had pubertal arrest. The cohort included girls >13 years and boys >14.5 years, who had absent onset of breast development in girls, testicular enlargement >4 mL in boys or no progressive pubertal change over at least 6 months. Exclusion criteria included use of oral glucocorticoids in the preceding 12 months, current vertebral fractures >Genant 3 found on spinal X-ray at screening, use of bisphosphonates or other bone modifying drugs in the last two years, contraindication to androgen or oestrogen use due to medication allergy, previous deep vein thrombosis or stroke related to coagulopathy. Both Institutional Ethics Committees approved the study.

Data collection and clinical measures

Phase 1 GMFCS was obtained from medical records. Participants were divided into two groups: predominantly ambulatory (GMFCS I–III) or non-ambulatory (GMFCS IV–V). Minimal trauma fracture was defined either as a self-reported or radiologically proven fracture occurring after a fall from standing height or less or a minimal trauma incident other than a fall (e.g. turning over in bed). Data were collected concerning current or past use of anticonvulsants, use of percutaneous endoscopic gastrostomy (PEG) feeding, age of commencement of sex-steroid therapy, the medication used, dosage and side effects if treated, Tanner stage, age of menarche for females, bone age reported by a radiologist using the Greulich and Pyle (GP) method, FSH, LH, oestradiol/testosterone, dual-energy X-ray absorptiometry (DXA), using a GE Lunar Prodigy (Madison, Wisconsin, software version 17). Interviews with patients who had sex-steroid treatment focused on bone and sexual health, medication compliance, tolerability and QoL (see Supplemental Material, Appendix 1). This was performed by one interviewer (AT).

Phase 2 Pubertal induction was commenced at baseline in a separate cohort of previously untreated patients. Pubertal status and progress were assessed every three months as per algorithm (Supplemental Material, Appendix 2). The primary outcome measure was bone density gain as assessed by lumbar spine height adjusted BMD over 24 months using DXA. Secondary outcomes were a reduction in fracture incidence as detected on spinal X-rays and self-reported long bone fractures, altered QoL, incidence of adverse events, pain and mobility using questionnaires. DXA scans were performed on a Hologic QDR 4500 Horizon DXA scanner (Hologic Inc., Bedford, MA).

Phase 2 puberty induction intervention

Induction of puberty was performed according to a proposed algorithm (Supplemental Material, Appendix 2). Boys were induced with transdermal testosterone commencing as 25 mg (½ sachet) Testogel® 50 mg sachets daily or 25 mg (2 actuations) of Testogel® pump, increasing slowly to 50 mg/day at 6 months, to a maximum of 100 mg/day at 12 months, to mimic normal pubertal progress. Girls were induced with transdermal oestrogen commencing at 0.5 mg oestradiol, increasing to 1 mg at 6 months to a maximum of 2 mg at 18 months or half a Climara® 25 patch weekly, to a maximum of Climara® 50 (3.8 mg oestradiol) patch at 18 months, to mimic normal pubertal progress. All dosing changes were based on clinical progress of puberty at each visit.

Results

Patient characteristics

For phase 1, 20 patients identified with delayed puberty were included in the clinical review, 14 female and six male. Mean BMI was 18.2 ± 6.4 g/cm^2. Sixteen of the twenty (80 %) were

Table 1: Participant characteristics.

	Phase 1 (n=20)	Phase 2 (n=10)
Female	14 (70 %)	6 (60 %)
Age, years, median (IQR)	18 (16.2–19.5)	15.0 (14.6–15.7)
Anticonvulsant use	10 (50 %)	9 (90 %)
Non-ambulatory	16 (80 %)	5 (50 %)
PEG fed	5 (25 %)	9 (90 %)
GMFCS		
II–III	4 (20 %)	1 (10 %)
IV	6 (30 %)	2 (20 %)
V	10 (50 %)	7 (70 %)
Treatment with sex-steroids	11 (55 %)	10 (100 %)

All expressed as n (%) unless otherwise stated.

non-ambulatory, with 50 % having a GMFCS of V. For phase 2, 10 participants were recruited into the study. Participant characteristics are shown in Table 1. Nine out of 10 participants were PEG fed in phase 2; all participants were taking adequate calcium supplementation whilst on this study. Investigators would monitor calcium and vitamin D supplementation (using dietary questions and blood tests) during this study and would intervene if either was low, but no intervention was necessary.

Puberty outcomes

In phase 1, the mean age of menarche was 17.8 ± 2.3 years, with one patient premenarchal at age 18. Eleven patients were treated with sex-steroids. Three had died at time of the study. Seven of the remaining eight families consented to an interview (five female, two male). All interviewees were mothers of the patients. Median time between treatment and interviews was 4 years (range 1–27).

Phase 2 participants utilised a proposed algorithm (Supplemental Material, Appendix 2) for pubertal induction with Tanner staging every three months (Table 2). Most patients (7/10) reached Tanner stage 3 by nine months. Only one participant reached Tanner stage 5 at 24 months.

Effects of hormone therapy, including adverse events

Phase 1: Eleven patients (55 %) received treatment. Reasons for not receiving treatment included parental concern regarding psychosexual effects of sex-steroids, late referral and better nutrition permitting onset of spontaneous puberty. All patients in phase 2 were treated with sex-steroid. Side effects and tolerability for both phases are detailed in Table 3. Worsening acne and irritability were reported in one male when oral testosterone undecanoate was increased from 160 to 240 mg daily. Carers of the two males denied any issues with aggression with testosterone replacement. For

Table 3: Side effects and tolerability for treatment in both phases.

Treatment	n	Side effects/tolerability
Oral oestradiol valerate and oral medroxyprogesterone acetate	3	n=1 spontaneous ovarian hyperstimulation syndrome (when on 2 mg oestradiol dose)
Transdermal oestradiol and oral medroxyprogesterone acetate	4	
Combined oral contraceptive pill	3	n=1 menorrhagia n=1 difficulty managing menses
Combined continuous transdermal patch	1	n=1 breakthrough bleeding
Oral testosterone undecanotate	4	n=1 worsening acne and irritability
1 % transdermal testosterone gel	2	
Transdermal testosterone patch	1	n=1 erythema site of patch
Sustanon, testosterone implants	1	n=1 difficulty with administration
Transdermal oestrogen patch	3	n=1 skin irritation
Trandsdermal oestrogen patch	3	n=1 vaginal bleeding

Table 2: Tanner staging for phase 2 participants (n=10) after induction as per the proposed algorithm (Supplemental Material, Appendix 2).

Participant	Gender	Visit date, months								
		Screening	3	6	9	12	15	18	21	24
1	M	1	1	2	2	3	4	W		
2	F	1	2	3	3	3	3	3	4	4
3	F	1	1	W#						
4	M	1	1	2	3	D				
5	F	1	2	3	3	4	4	4	4	4
6	M	1	1	2	3	3	3	3	3	3
7	F	1	2	3	3	4	4	4	4	5
8	M	1	2	2	2	2	2	W		
9	F	2	2	2	3	3	3	W		
10	F	2	3	3	3	W				

D, died; W#, withdrew due to fractures; withdrew for other reasons. Treatment was started at a low dose, increasing incrementally based on clinical pubertal changes over 3-month intervals.

females using HRT, mild worsening mood (n=2) and possible improvement in cognition (n=1) were described. No difficulty with menstrual management was reported.

Phase 2: Participants tolerated treatment very well, with no reports of breast tenderness, no aggressive behaviour or inappropriate masturbation in public for either sex (previously reported by families as an adverse outcome). Three participants had mild skin irritation related to patches. Three female participants experienced intermittent vaginal bleeding. One male participant disliked the gel and was switched to IM therapy. Treatment adherence was monitored by a treatment diary showing a compliance rate of above 80 %.

Bone outcomes

For phase 1, LS BMD was too variable to draw any major conclusions, percentage change in BMD per year ranging from −4.8 to +36 % over 1–4 years for males and 0.54–5.76 % for females. Eleven patients from the phase 1 cohort had bone age X-ray, with a mean delay in bone age of 4.1 ± 2.2 years. Growth hormone assessment was not available for most patients, so contribution of growth hormone deficiency to the delay could not be excluded. Vitamin D levels were not regularly recorded. Eight patients (40 %) had a prevalent fracture, and five experienced multiple fractures, all with minimal trauma, predominantly involving the lower limb (55 %), the remainder involving the upper arm (n=2), clavicle (n=2) and spine (n=1).

In phase 2, DXA scans were challenging to measure in this population as many patients were unable to stay still for scanning. Only six patients could be scanned. DXA reports of participants who had withdrawn and stopped treatment were also collected. LS BMD% changes were negligible in phase 2, ranging from 0.15 to 0.24 % per year, remaining stable over 1–2 years in all who could be scanned. One participant was withdrawn from the study after 6 months due to two minimal trauma femoral fractures requiring bisphosphonate. One male had a left femoral fracture documented straight after starting testosterone therapy. No other phase 2 participants had documented vertebral or long bone fractures during the intervention period.

Pain and mobility outcomes

Pain and mobility outcomes could only be measured in the phase 2 cohort. For families who completed the questionnaires, baseline QoL scores (out of 120) ranged from 62 to 92 (n=5), and 24 month QoL scores ranged from 80.5 to 92 (n=5). Mobility was maintained in all previously ambulant patients (n=5), with IPAQ results showing that over 24 months, all ambulant participants could maintain the same number of minutes conducting activities such as walking, except one participant who doubled their activity minutes from baseline (30–60 min per week).

Discussion

Near 50 percent of all bone mass is accrued during puberty, the total accrued [17], determining peak bone mass (PBM) by the end of puberty, a significant determinant of osteoporosis and fracture risk later in life [18]. Delayed puberty is associated with lower BMD and increased fracture risk [19]. Adult hypogonadism results in low BMD in a normal population, ameliorated by sex-steroid replacement [20–22]. The importance of sex-steroids for bone accrual and maintenance has not been formally demonstrated in those with CP, although the same principles apply to this group. Meaningful data collection for large numbers of this disparate group has proved very difficult. Therefore, our recommendations are based on data we could obtain in our two cohorts, together with the previously reported limited evidence. Most participants in the retrospective cohort (phase 1) were referred to endocrinologists because of bone health concerns: delayed or arrested puberty having either been missed, not assessed or not recognised by carers or health professionals and thus not considered to be related to low bone density. Further contributors to impaired bone health included inadequate nutrition, low BMI, plus possible inadequate vitamin D and calcium intake.

In multivariable analysis, low body fat has been reported to independently predict delayed skeletal age in children with CP [14]. Optimising nutrition, therefore, may positively impact bone health in CP, permitting improved hypothalamic pituitary gonadal (HPG) axis function, independent progress through puberty and maintenance of the adult HPG axis. We recommend that Tanner staging be performed as part of the routine paediatric assessment in CP. In addition, lack of menses in females should alert carers and clinicians to possible delayed puberty, with careful attention to dietary history and micronutrient intake as contributors. This represents an opportunity for screening for sex-steroid deficiency and provides a rationale for treatment.

Although most of the phase 1 cohort were reported to accept and tolerate sex-steroid treatment without adverse effects, attempted data collection demonstrated marked variability in the underlying cause of CP, degree of immobility, with inconsistencies in investigation and treatment modalities. However, GMFCS level was more severe in those

with hypogonadism. Phase 1 results showed sex-steroid dosing to be inconsistent and less than standard HRT, probably contributing to inconsistent data regarding changes in BMD. No patients received a progestogen-bearing intrauterine device or depot progestogen combined with oral/transdermal oestrogen, which are suggested options for menstrual management in those with a disability [23].

These difficulties were reflected in the prospective cohort (phase 2), where hurdles to consistent documentation included minimal recruitment despite extensive attempts within several hospital departments, confounders of multiple concomitant medications, cerebrovascular accident, demise in 3 of 10 and inability to perform pQCT or DXA due to movement artefact or presence of orthopaedic instrumentation. Thus, data obtained were fragmentary and not statistically assessable. In addition, the carer demands on families were enormous, impairing any ability to comply with the study conditions.

Limitations

For phase 1, limitations included the retrospective nature of the data, limited bone density data to support a benefit of HRT and the inability to contact several families to confirm the documented history. Similarly, for phase 2, despite intensive attempts over 4 years to recruit families across several paediatric disciplines of developmental medicine, neurology and general pediatrics, only 10 participants agreed; of those, loss to follow up, withdrawal from treatment due to contending priorities and death further reduced the numbers.

For those who were eligible, no one refused treatment, suggesting the uptake of non-invasive pubertal induction is appealing to parents, and they see the benefit of optimised bone health. This study used lumbar spine as a marker for bone health, which is the most commonly used marker but limits our understanding regarding other clinically relevant sites. Future research will be aimed at following these patients prospectively, to assess longitudinal effects of the intervention.

In summary, delayed puberty and hypogonadism may be poorly recognised in CP leading to late diagnosis. Both assessment and interventions are hampered by multiple complex factors. Assessment of bone health in CP should include screening for sex-steroid deficiency, which is more common in those with a poor functional status. Optimisation of nutritional status and replacement of sex-steroids or use of pubertal induction where indicated is likely to improve bone health and to reduce adult osteoporosis.

Acknowledgments: The study team would like to thank all the participants who volunteered their time to participate in this study. The study team would also like to thank A/Prof Peter Simm and Dr Gabby Atlas for helping with the occasional study visit.

Research ethics: The research related to human use has compiled with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration, and has been approved by The Royal Children's Hospital Human Research and Ethics Committees (Project no: HREC 36302).

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: All authors meet all 4 criteria of authorship outlined by ICMJE. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: All authors declare no competing interests.

Research funding: This work has been supported by a Cerebral Palsy Alliance Research Foundation Grant (ERG01119) and The Perpetual Trustee's Impact philanthropy application program (IPAP2017/0690). The funding organisations played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report or in the decision to submit the report for publication.

Data availability: The raw data can be obtained on request from the corresponding author.

References

1. Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet 2014;383:1240–9.
2. Cremer N, Hurvitz EA, Peterson MD. Multimorbidity in middle-aged adults with cerebral palsy. Am J Med 2017;130:744 e749–15.
3. Trinh A, Wong P, Fahey MC, Brown J, Churchyard A, Strauss BJ, et al. Musculoskeletal and endocrine health in adults with cerebral palsy: new opportunities for intervention. J Clin Endocrinol Metab 2016;101:1190–7.
4. Henderson RC, Kairalla J, Abbas A, Stevenson RD. Predicting low bone density in children and young adults with quadriplegic cerebral palsy. Dev Med Child Neurol 2004;46:416–9.
5. Houlihan CM. Bone health in cerebral palsy: who's at risk and what to do about it? J Pediatr Rehabil Med 2014;7:143–53.
6. Kuperminc MN, Gurka MJ, Houlihan CM, Henderson RC, Roemmich JN, Rogol AD, et al. Puberty, statural growth, and growth hormone release in children with cerebral palsy. J Pediatr Rehabil Med 2009;2:131–41.
7. Robertson CM, Morrish DW, Wheler GH, Grace MG. Neonatal encephalopathy: an indicator of early sexual maturation in girls. Pediatr Neurol 1990;6:102–8.
8. Bruzzi P, Messina MF, Bartoli A, Predieri B, Lucaccioni L, Madeo SF, et al. Central precocious puberty and response to GnRHa therapy in children

with cerebral palsy and moderate to severe motor impairment: data from a longitudinal, case-control, multicentre, Italian study. Int J Endocrinol 2017;2017:4807163.
9. Worley G, Houlihan CM, Herman-Giddens ME, O'Donnell M, Conaway M, Stallings VA, et al. Secondary sexual characteristics in children with cerebral palsy and moderate to severe motor impairment: a cross-sectional survey. Pediatrics 2002;110:897–902.
10. Uday S, Shaw N, Krone R, Kirk J. Hypopituitarism in children with cerebral palsy. Arch Disease Child Educ Pract Ed 2017;102:559–61.
11. Golden NH, Lanzkowsky L, Schebendach J, Palestro CJ, Jacobson MS, Shenker IR. The effect of estrogen-progestin treatment on bone mineral density in anorexia nervosa. J Pediatr Adolesc Gynecol 2002;15: 135–43.
12. Strokosch GR, Friedman AJ, Wu SC, Kamin M. Effects of an oral contraceptive (norgestimate/ethinyl estradiol) on bone mineral density in adolescent females with anorexia nervosa: a double-blind, placebo-controlled study. J Adolesc Health 2006;39:819–27.
13. Misra M, Katzman D, Miller KK, Mendes N, Snelgrove D, Russell M, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Min Res 2011;26:2430–8.
14. Henderson RC, Gilbert SR, Clement ME, Abbas A, Worley G, Stevenson RD. Altered skeletal maturation in moderate to severe cerebral palsy. Dev Med Child Neurol 2005;47:229–36.
15. Pfeil A, Haugeberg G, Renz DM, Reinhardt L, Jung C, Franz M, et al. Digital X-ray radiogrammetry and its sensitivity and specificity for the identification of rheumatoid arthritis-related cortical hand bone loss. J Bone Miner Metabol 2017;35:192–8.
16. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23.
17. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Min Res 2018;33:190–8.
18. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. J Bone Min Res 2017;32:1291–6.
19. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int 2017;28:1723–32.
20. Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82:2386–90.
21. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone replacement therapy versus the combined oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. J Clin Endocrinol Metab 2016;101: 3497–505.
22. Popat VB, Calis KA, Kalantaridou SN, Vanderhoof VH, Koziol D, Troendle JF, et al. Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. J Clin Endocrinol Metab 2014;99:3418–26.
23. Zacharin MR. Puberty, contraception, and hormonal management for young people with disabilities. Clin Pediatr 2009;48:149–55.

Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/jpem-2024-0013).