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REVIEW

Induction of puberty in hypogonadal forms of primary amenorrhoea: current evidence and future perspectives

Eriselda Profka[1,2], Giulia Rodari[2], Valeria Citterio[2], Valentina Collini[1,2], Aurora Pedroli[1,2], Giovanna Mantovani[1,2] and Claudia Giavoli[1,2]

[1]Department of Clinical Sciences and Community Health, Department of Excellence 2023–2027, University of Milan, Milan, Italy
[2]Endocrinology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Correspondence should be addressed to C Giavoli: claudia.giavoli@unimi.it

Abstract

Primary amenorrhoea is defined as the absence of spontaneous menarche by the age of 15 years with normal pubertal development or of 13 years in the absence of pubertal signs. The aim of this review was to provide a comprehensive overview of current evidence on puberty induction in girls with primary amenorrhoea, to highlight clinical practices, and to identify directions for future research. Puberty induction aims not only to achieve secondary sexual characteristics but also to ensure an appropriate growth spurt and attainment of final adult height, optimal peak bone mass achievement, uterine development and maturation, and psychosocial well-being. Oestrogen therapy (preferably oral or transdermal 17β-oestradiol), initiated at low doses and gradually increased, remains the cornerstone of treatment for girls with absent or arrested puberty. Progesterone is usually introduced after 18–24 months or following spontaneous bleeding to prevent endometrial hyperplasia, although timing should be individualized according to uterine response to oestrogen. Clinical evidence indicates that premature progestin introduction should be avoided to allow complete uterine and breast development; therefore, a patient-centred approach tailored to individual characteristics is essential. Moreover, reproductive technologies have expanded fertility options for women with either central hypogonadism or premature ovarian insufficiency. In this context, a tailored approach aimed at achieving optimal uterine development is crucial. Most available data derive from Turner syndrome cohorts and small observational studies, underscoring the need for individualized protocols. Importantly, future research should further investigate bone metabolism and psychosocial aspects, with the goal of refining clinical practice in pubertal induction.

Keywords: primary amenorrhoea; puberty induction; hypogonadism

Introduction

Primary amenorrhoea is defined as the absence of spontaneous menstruation by the age of 15 in girls who exhibit normal growth and pubertal development, or within five years from the onset of thelarche (1, 2). Furthermore, the evaluation of primary amenorrhoea should be undertaken in the absence of spontaneous menstrual bleeding in a girl aged 13 years or older who shows no signs of pubertal development (3).

Primary amenorrhoea reflects the inability of the hypothalamic–pituitary–gonadal (HPG) axis to generate the cyclic endometrial changes necessary for menstruation. However, it may also result from the absence of effector organs

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(uterus or vagina) or from outflow obstruction due to anatomical anomalies of the vaginal canal.

It is important to emphasize that primary amenorrhoea is not a disease in itself, but rather a clinical symptom that may be associated with a wide variety of conditions. Its aetiology can be broadly classified into anatomical, ovarian, hypothalamic, pituitary, and other endocrine causes, as well as multifactorial conditions (2).

Within the hypogonadal spectrum, two main categories can be distinguished: hypogonadotropic hypogonadism (HH), due to impaired gonadotropin secretion, and hypergonadotropic hypogonadism, resulting from primary gonadal failure (Table 1). Each of these forms presents distinct pathophysiological mechanisms, diagnostic features, and therapeutic challenges.

Notably, in the past decades, the late effects of antineoplastic treatments have emerged as an increasingly recognized cause of HPG axis dysfunction (4). Hypogonadism is a frequent finding after cancer therapy and may result either from primary gonadal injury (premature ovarian insufficiency, POI) or from impaired gonadotropin secretion secondary to hypothalamic–pituitary damage. The clinical approach to this patient group is usually extrapolated from studies on gonadal failure of various aetiologies, rather than being tailored to the specific clinical features and needs of childhood cancer survivors (CCSs), who represent a particularly vulnerable population often burdened by multiple concomitant comorbidities (4).

This review addresses hypogonadal forms of primary amenorrhoea, whereas genetic anomalies or

Table 1 Major causes of primary hypogonadal amenorrhoea.

Anatomical dysfunction level	Conditions	Key mechanism
Hypothalamic dysfunction	Isolated congenital GnRH deficiency (±anosmia) Functional hypothalamic amenorrhoea (eating disorders, excessive exercise, excessive stress, psychiatric diseases, chronic diseases (e.g. celiac disease and inflammatory bowel disease) Inflammatory or infiltrative diseases (e.g. haemochromatosis and sarcoidosis) Brain tumours (e.g. astrocytoma, craniopharyngioma, and germinoma) Cranial irradiation Traumatic brain injury Syndromic conditions (charge syndrome, Prader–Willi syndrome, Laurence–Moon syndrome, Gordon Holmes syndrome, Bardet–Biedl syndrome, etc.)	↓ GnRH secretion
Pituitary dysfunction	Pituitary tumours/hyperprolactinaemia Genetic conditions Inflammatory or infiltrative diseases (e.g. autoimmune hypophysitis, haemochromatosis, sarcoidosis, Langerhans cell histiocytosis, and granulomatous diseases) Empty sella (primary or secondary) Pituitary apoplexy Infections Surgery/radiation	↓ FSH/LH levels
Ovarian dysfunction	Primary ovarian insufficiency (e.g. autoimmune aetiology) Gonadal dysgenesis/agenesis (e.g. mutations in SRY, NR5A1, DHH, FOG2/ZFPM2, and WNT1) Chemotherapy/radiotherapy Surgery Steroidogenic enzymes mutation (e.g. CYP17A1 mutation) FSH or LH receptor mutation	Gonadal failure, ↑FSH/LH levels due to the lack of negative feedback of oestrogen and inhibin B on pituitary gland
Others	Polycystic ovary syndrome (rare, mostly secondary amenorrhoea) Hyper- and hypothyroidism Exogen androgen use/Cushing's syndrome Medications (e.g. opioids)	Hormonal imbalance and metabolic dysfunction

GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle- stimulating hormone; CYP17A1, steroid 17-alpha-hydroxylase/17,20-lyase.

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malformations of the reproductive tract, such as Müllerian agenesis or complete androgen insensitivity syndrome, are beyond its scope.

Induction of puberty in hypogonadal girls is a cornerstone of clinical management, aiming not only to promote secondary sexual characteristics development but also to guarantee an appropriate growth spurt and a final adult height consistent with mid-parental height, an optimal bone mineralization, an appropriate uterine development and maturation, and psychosocial well-being (5, 6, 7, 8). Current management approaches emphasize a gradual introduction of oestrogen therapy, subsequently combined with progesterone, tailored to individual aetiology and patient characteristics (6, 8, 9, 10). Despite established protocols, several challenges persist, including optimization of dosing regimens, timing of therapy, and long-term outcomes (11).

This review aims to provide a comprehensive overview of current evidence on puberty induction in girls with primary amenorrhoea, highlight established practices, and identify directions for future research.

From physiology to pathology

Puberty represents one of the most fascinating and still mysterious transitions in human development. The onset of puberty marks the end of childhood and the beginning of a process ultimately leading to reproductive capacity: a transformation involving intricate neuroendocrine regulation and coordinated changes across multiple systems.

Despite decades of research, the exact mechanisms that trigger puberty remain incompletely understood. In girls, pubertal development typically begins between 8 and 13 years of age. The first visible sign is usually breast development, followed by the appearance of pubic hair and menarche within two to three years (12). The transition from Tanner stage B1 to B2 is driven by pulsatile secretion of luteinizing hormone (LH), induced by gonadotropin-releasing hormone (GnRH), which initially occurs at night. The hypothalamic neural substrate that generates the pulsatile GnRH release is known as the 'GnRH pulse generator', primarily driven by specialized hypothalamic neurons called KNDy cells, which coordinate the release of gonadotropin through the interplay of three key neuropeptides: kisspeptin, neurokinin B, and dynorphin (13). Nutrition, including intrauterine influences and adipocyte-derived hormone (i.e. leptin), appears to help set the biological clock, but no single factor has been identified as the ultimate initiator of this complex process (14). Adequate maturation of secondary sexual characteristics is achieved with oestrogen alone, while progesterone rises only in the late stages of puberty supporting both endometrial differentiation and lobulo-alveolar breast development (8, 15). In the breast, progesterone acts through the progesterone receptor in coordination with oestrogen, with the highest rate of epithelial proliferation occurring during the luteal phase, when progesterone levels peak (15). Moreover, oestrogens exert a synergistic effect on the GH–IGF-1 axis by enhancing hypothalamic–pituitary GH secretion and potentiating peripheral IGF-1 activity at the growth plate, thereby amplifying pubertal growth spurt (16).

Disturbances in the physiological process of puberty can lead to absent or arrested pubertal development, primary amenorrhoea, and infertility, regardless of whether the underlying cause of hypogonadism is primary (ovarian failure) or secondary (central hypothalamic–pituitary dysfunction).

In such conditions, pubertal induction becomes essential to mimic natural development and support both physical and psychological well-being.

When and how to induce puberty

The aim of pubertal induction in girls with hypogonadism is to mimic natural puberty, promoting the development of secondary sexual characteristics, growth, peak bone mass acquisition, and adequate uterine maturation, the latter being crucial for future childbearing potential (6, 7, 8, 17).

In females, the therapeutic approach tends to be relatively more straightforward than in males, since the keystone of management, regardless of whether the hypogonadism is hypogonadotropic or hypergonadotropic, consists of oestrogen administration followed by progestin (8).

Puberty induction through continuous GnRH administration has been proposed by some authors (18), although the available evidence is scarce, and standardized or validated treatment protocols are not yet established.

However, in practice, tailoring the timing, dosage, and formulation to mirror physiological progression is the major challenge. Thus, pubertal induction cannot follow a 'one-size-fits-all' model; it must be carefully individualized according to each patient's condition, physiological state, and emotional context.

Ensuring timely initiation of puberty induction is essential for physiological development, despite the lack of international consensus on the optimal starting age. A recent international survey of 229 healthcare professionals from 45 countries, predominantly paediatric endocrinologists, revealed significant variability in clinical practice. More than half reported initiating oestrogen therapy between ages 10 and 12, typically over a 2- to 3-year induction period, with differences related to drug availability, patient characteristics, and clinical experience (19). Current evidence suggests that in girls without an identified

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cause of hypogonadism, the absence of pubertal signs by age 13 should prompt diagnostic evaluation and consideration of pharmacological induction. In patients with a known cause of hypogonadism, induction may be started around 11 years of age (10). Indeed, delayed pubertal induction may independently increase the risk of low bone mineral density and psychosocial issues (10). On the contrary, literature data on the impact of late pubertal induction on complete development of secondary sexual characteristics are inconclusive, since long-term outcomes appear to be influenced more by oestrogen formulation, dose and titration, and achieved hormone levels than by timing of initiation alone (9, 20, 21).

Puberty induction should begin with low-dose oestrogen replacement, gradually increased to achieve complete pubertal development. This process can be divided into two phases: the first, characterized by low oestrogen doses, is crucial for initiating pubertal growth and physiological breast development; the second, with higher doses, is essential to finalize bone mass accrual and uterine maturation (8, 9, 10). Moreover, the optimal route of administration, drug choice, dosing, and schedule should be individualized. For example, in cases of delayed diagnosis or pubertal arrest with spontaneous onset, a slightly faster escalation of oestrogen dosage may be considered, depending on the individual clinical profile and growth potential (8, 10, 20).

The individualization of therapy is extremely challenging, as most available evidence on pubertal induction derives from studies in Turner syndrome cohorts, limiting the generalizability of findings to other populations with specific clinical features. Current induction regimens rely largely on data from physiological puberty, isolated clinical experiences, and small observational or interventional studies. In addition, the oestrogen formulations currently employed (synthetic, conjugated, and natural) are all off-label in pubertal age, since distinct efficacy and safety profiles have been extensively characterized only in postmenopausal or adult women.

Oestrogen formulations

As previously outlined, oestrogen is the primary driver of secondary sexual maturation in girls, while progesterone plays a later, modulatory role (8, 15).

To date, several studies in the literature support the effectiveness and theoretical benefits of starting pubertal induction with low-dose oestradiol, being more physiological than ethinyl-oestradiol (EE, a very potent synthetic analogue that is not metabolized to oestradiol). Natural oestradiol (E2, either oral or transdermal) is safer and more effective, with lower thrombotic and hypertensive risk and superior feminization effect and clinical efficacy (22, 23, 24). In addition, E2 gives the advantage of being titrated according to oestradiol serum levels that can be easily measured during treatment.

On the contrary, EE is a synthetic analogue with significantly higher bioavailability and greater plasma stability due to the 17α-ethinyl substitution, which renders it resistant to hepatic metabolism and consequently prolongs its systemic availability. Nevertheless, due to its continuous hepatic exposure, EE induces significant changes in hepatic and systemic parameters (including induction of procoagulant factors, sex hormone-binding globulin (SHBG), cortisol-binding globulin (CBG), and renin, as well as reduction of IGF-1) (25). Accordingly, EE formulations have been associated with an increased thromboembolic risk, alterations in lipid profile, and activation of the renin–angiotensin system with blood pressure effects along with modifications in the bioavailable fractions of androgens and corticosteroids (25, 26). In addition, EE cannot be measured during treatment. For all the above-mentioned reasons, there is a general consensus against the use of EE in the induction of puberty.

Similarly, conjugated equine oestrogens (CEEs), which are of animal origin (derived from purified urine), exert fluctuating biological effects due to their heterogeneous composition of multiple oestrogenic compounds (27).

As for the administration route, the transdermal oestradiol bypasses hepatic metabolism, exerts neutral effects on lipids and coagulation, avoids the variability in intestinal absorption, and allows easy dose titration via patch division (28, 29). In addition, with a patch, it is also possible to monitor the duration of attachment, thus mimicking the normal diurnal/nocturnal variations in oestradiol typical of early puberty. Moreover, transdermal oestradiol causes less IGF-1 suppression and SHBG induction, maintaining a more physiological oestradiol/oestrone ratio and reducing genotoxic metabolite accumulation (28, 29, 30). It also seems to exert more positive effects on cardiovascular risk markers and bone mineral density (31). All in all, despite practical limitations in adolescents, such as patch detachment, transdermal oestradiol should be considered the first-line option for the reasons outlined above. However, oral oestradiol may be considered in certain circumstances, such as in cases of skin damage/intolerance or when adherence to treatment is a concern.

It is important to underline that, to date, no standardized induction regimen exists, although several are widely used (20, 23, 24, 32, 33, 34, 35, 36, 37). Some authors have proposed starting pubertal induction with low overnight growth promoting doses of oestradiol, which are then progressively increased in order to achieve a more physiological development (20, 32, 38, 39). The protocol proposed by Davenport starts with low-dose transdermal oestradiol (0.1 μg/kg overnight), increasing semi-annually over 18–24 months to mimic physiological

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puberty (32). Faster regimens for late diagnoses (e.g. 12.5 μg/24 h initially and then 25 μg/24 h until withdrawal bleeding) have shown to ensure satisfactory progression of secondary sexual characteristics without impairing growth or uterine volume (35). As for oral oestradiol, the protocol proposed by Delemarre (5 μg/kg gradually increased over 2–3 years up to the adult dose of approximately 2 mg) (33) and simplified fixed-dose schemes (37, 40) are effective alternatives. Calculating a weight-based dose can be complex unless a compounding pharmacy is available to prepare custom formulations. However, the study by Labarta demonstrated that using a standard fixed dose does not compromise efficacy or safety compared with individualized dosing (37). Therefore, treatment can be simplified as suggested by Zacharin, starting with half a tablet (0.5 mg) on alternate days and progressively increasing the dose until reaching the adult level (40).

Progestins

While induction with oestrogen alone is possible, prolonged lack of progesterone increases the likelihood of endometrial complications, such as hyperplasia, endometriosis, and cancer (41, 42). Consequently, progesterone should be introduced, generally after 18–24 months or once spontaneous bleeding occurs. Nonetheless, the optimal timing should be tailored to the individual's uterine response to oestrogen therapy and clinical context, as available data suggest that premature progesterone introduction may hamper subsequent breast and uterine development (20, 43, 44). Progesterone administration is mandatory at bleeding occurrence, but only if adult breast and uterine conformation has been achieved. Pelvic ultrasound should be performed during pubertal induction and upon completion to document uterine size and shape and to evaluate the endometrial thickness, thereby guiding the optimal timing for progestin initiation. As for size, a uterine cut-off of 65 mm is commonly used to define maturity, based on the normative data by Griffin *et al.* (45). However, uterine maturation should be assessed comprehensively, considering uterine morphology (transition from tubular to pear-shaped configuration) and corpus-to-cervix ratio (21). If breakthrough bleeding occurs in association with ultrasound evidence of endometrial thickening in the presence of underdeveloped breasts or uterus, a slight reduction in oestradiol dose should be considered before introducing progestins. Moreover, data on uterine maturation indicate that increasing oestradiol dose could be ineffective in certain patients with poor uterine response, particularly those with a history of pelvic irradiation, while potentially exposing them to a higher risk of adverse effects (20).

Options include medroxyprogesterone acetate (MPA), micronized progesterone, and dydrogesterone. MPA, though effective, is non-selective for progesterone receptor, and its androgenic and glucocorticoid effects may increase thromboembolic and metabolic risks. Some authors suggest that androgenic progestins, such as norethisterone, may impair normal uterine maturation and development (43, 46), probably due to their widely documented antiproliferative effects on the endometrium (47). For this reason, they may not be considered first-line agents for pubertal induction. Micronized progesterone, bioidentical to endogenous hormone, shows better metabolic and coagulative safety; dydrogesterone shares similar properties and has been included among the suggested progestins by the European Society of Human Reproduction and Embryology (48), even though no studies so far have analysed its endometrial effects in patients with hypogonadism. Although data in adolescents are scarce, micronized progesterone or dydrogesterone should be preferred, administered sequentially for 14 days per month (micronized progesterone 100–200 mg/day or dydrogesterone 10 mg/day) (9, 10, 49). Alternatively, continuous progestin administration can also be offered to patients who do not desire menstrual bleeding. However, cyclic administration offers the benefit of enabling earlier pregnancy detection. Since women with hypogonadism may rarely ovulate spontaneously, any missed withdrawal bleed should prompt immediate pregnancy testing.

In clinical practice, combined formulations containing both oestrogen and progesterone, either oral or transdermal, may be used when the introduction of progesterone is indicated and may be preferred by some girls. On the contrary, European consensus guidelines for HH advise against the use of combined oral contraceptives (COCs) for pubertal induction as they do not mimic the physiological progression of puberty and contain supraphysiological doses of oestrogens (50). Recent evidence indicates that COCs are inferior to physiological oestrogen replacement in terms of bone mineral density improvement, uterine development, and long-term cardiometabolic outcomes, particularly in older females (50). However, even so, COCs are still preferable to receiving no therapy.

The most used puberty induction protocols are summarized in Table 2.

Clinical and uterine outcomes

Clinical and uterine outcomes at the end of the induction can wary widely according to the underlying cause of hypogonadism (4, 20). At the aim of mimicking natural puberty, it is of paramount importance to consider two main outcomes, namely,

Table 2 Most commonly used puberty induction protocols in girls with hypogonadism.

Author/study	Route of administration	Starting dose	Increment/target E2 level (pg/mL)	Duration/target	Notes
Davenport (32)	Transdermal (E2 patch)	0.1 μg/kg (overnight – cut and apply part of a matrix patch delivering this dose; apply in p.m. and remove in a.m.)→ target E2 levels 3–4 pg/mL	Dose doubled every 6 months continuously: 0.1 μg/kg→ 0.2 μg/kg → 12.5 μg→ 25 μg → 37.5 μg → 50 μg* → 75 μg → 100 μg Target E2 levels, respectively, 3–4 → 6–8 → 12 → 25 → 37 → 50 → 75 → 100† pg/mL	18–48 months	Gradually increase patch size according to body weight until target E2 levels are reached
Ankarberg *et al.* (38)	Transdermal (nocturnal)	0.05–0.07 μg/kg	Gradual increase based on E2 levels	2–3 years	Mimics early-pubertal E2 levels (1.9–6.5 pg/mL); if breast development prioritized: 0.08–0.12 μg/kg
Gawlik *et al.* (35)	Continuous transdermal	12.5 μg/24 h for 2 months	After the first 2 months, 25 μg/24 h until breakthrough bleeding Patches changed twice weekly	Until breakthrough bleeding, then switch to cyclic oestrogen + progesterone therapy	'Rapid' protocol for late-diagnosed cases; good pubertal and uterine progression; growth potential non-compromised
Zacharin *et al.* (40)	Transdermal	¼ of a 25 μg patch	Slow increase	2–3 years‡	Same dose applied midweek
Delemarre *et al.* (33)	Oral (17*β*-oestradiol) Oral ethinyl-oestradiol (EE)	5 μg/kg/day 0.1 μg/kg/day	Doubled every 6 months (5 → 10 → 15 → 20 μg/kg) Doubled every 6 months (0.1 → 0.2 → 0.4 → 0.6 μg/kg, adult ≈30 μg/day → switch to combined OCP)	2 years (up to 2 mg/day of adult dose) 2 years (up to 30 μg/day of adult dose	Oral alternative to transdermal approach
Labarta *et al.* (37)	Oral (17*β*-oestradiol)	FD: 0.2 mg/day ID: 5–15 μg/kg/day, adjusted by BA and tanner stage	Increased to 0.5 mg/day after 1 year	2 years	Efficacy of FD comparable to ID regimens; FD resulted simple, practical, and well tolerated
Zacharin *et al.* (40)	Oral (17*β*-oestradiol)	0.5 mg every other day for 3 months	Then 0.5 mg/day for 6–9 months→1 mg/day for 1 year→ finally adult dose 2 mg/day	2–3 years‡	Simplified step-up schedule for practical use

E2, oestradiol; OCP, oral contraceptive pill; FD, fixed dose; ID, individualized dose.
*Start progestin (earlier, if breakthrough bleeding occurs). †Typical adult dose. ‡After ≥1 year, introduce medroxyprogesterone acetate 10 mg/day or norethisterone 5 mg/day for 12–14 days every 1–3 months.

a gradual and complete breast development and an appropriate uterine maturation, given their crucial role in establishing self-esteem and in ensuring future opportunity of pregnancy.

Oestrogens are the principal drivers of these maturational processes, stimulating breast tissue growth and promoting uterine transformation from a tubular to a mature pear-shaped configuration,

with consequent increases in size and volume, thus opening new future possibilities for conception (21). Indeed, advances in reproductive technologies now allow many women with central hypogonadism and some with POI to achieve pregnancy, either through fertility preservation or egg donation (50, 51). Studies have shown that insufficient uterine development, marked by a shorter uterine length, a thin endometrium, or poor vascularization, may adversely affect pregnancy outcomes (21, 52). However, some authors have shown that final uterine length after induction remains significantly lower in hypogonadal patients compared to healthy controls (21). The adequacy of oestrogen therapy and the timing of progesterone introduction seem to be the two main factors determining breast and uterine development. In a recent retrospective study on final uterine size in hypogonadal females, it was concluded that optimal uterine growth during pubertal induction depends on the use of physiological 17β-oestradiol and on the maintenance a prolonged unopposed oestrogen phase (around three years) before adding progesterone. This approach seems to prevent premature arrest of uterine growth (53).

A recent multicentre study investigated the outcomes of pubertal induction with transdermal 17β-oestradiol in 95 hypogonadal girls, including CCSs (20). The study assessed auxological and uterine parameters to identify factors influencing optimal pubertal and reproductive development. At the end of induction, approximately 90% of patients achieved Tanner stage IV, while complete breast maturation (Tanner stage V) occurred in only 41% of girls. Achievement of Tanner stage V was significantly associated with the transdermal 17β-oestradiol dose at the time of progesterone introduction. Similarly, uterine longitudinal diameter increased progressively during oestradiol therapy, and by the end of induction, 74% of patients achieved an adult uterine shape. However, only 38% of cases achieved a mature uterine length (>65 mm). Conversely, pelvic irradiation emerged as the main factor impairing uterine development, regardless of the hormonal regimen. Importantly, the study found that no further uterine growth occurs once progesterone is introduced, suggesting that premature administration of progestins may hinder uterine and breast maturation (20).

On the basis of these findings, pelvic ultrasound prior to progesterone initiation should be regarded as standard clinical practice. In selected cases, as discussed above, a slight reduction in 17β-oestradiol dose may be considered before adding progestins, although this strategy requires confirmation in larger studies. Reinforcing the need for an individualized therapeutic approach, current results also suggest that escalating transdermal 17β-oestradiol before progestin initiation, with the aim of optimizing uterine outcomes, may be entirely ineffective in certain patients with poor uterine response to oestrogen replacement therapy and a history of bone marrow transplantation or pelvic irradiation. In this context, dose escalation may prove not only futile but also potentially harmful in CCSs, who represent 'poor responders' to oestrogen and are at increased risk of secondary neoplasms.

As previously reported, some authors advocate initiating pubertal induction with overnight low-dose transdermal oestradiol, followed by stepwise dose escalation to emulate early-pubertal oestrogen levels and their diurnal profile (20, 32, 38, 39). This approach aims to promote progressive breast maturation and enhance growth velocity. Although no regimen has proven superior, some evidence indicates that low-dose induction, including overnight-only oestradiol, may support height gain during the first year of treatment and at adult height. However, in specific cases with delayed diagnosis, this approach may reasonably be avoided to prevent further treatment delay (20).

These results emphasize the importance of an individualized and physiology-based approach to pubertal induction, tailoring both oestrogen dose escalation and progesterone timing according to clinical and ultrasound findings to optimize long-term reproductive potential.

Personalized induction allows optimization of both physical and emotional outcomes, respecting each patient's developmental needs and expectations.

Challenges and future directions

Despite significant advances in pubertal induction strategies, several challenges remain regarding the optimal availability, dosing, and formulation of sex steroid preparations worldwide. The recent survey by Gawlik-Starzyk, which investigated the global availability, usage, and preferences of oestradiol and progestogen preparations used for puberty induction, showed that low-dose formulations suitable for gradual pubertal induction remain scarce. Only a few countries reported access to 0.5 mg oestradiol tablets or patches delivering 14–25 μg per day, while most available products were adult-strength formulations, such as 50 μg patches or 1–2 mg tablets (19). Overall, the study underscores substantial global disparities in access to appropriate low-dose oestradiol necessary for physiological pubertal induction. The predominance of adult-strength products often forces clinicians to modify doses or resort to off-label strategies to mimic physiological puberty (19).

Further research should address bone mass increase and psychosocial outcomes during induction.

Oestrogens exert a dual effect on bone: low doses promote linear growth, while high doses induce epiphyseal cartilage fusion. Almost half of total bone mass is gained during puberty, a period of accelerated skeletal

growth in both length and strength (54). As observed by Heaney, failure to achieve peak bone mass within this critical window represents an important risk factor for osteoporosis and fractures in adulthood (55). Moreover, studies have shown that puberty timing is a critical determinant of peak bone mass and lifelong skeletal health, suggesting that people who experience later puberty may be at increased risk of lower bone density and osteoporosis in later life (56). Accordingly, the timing of induction must be carefully calibrated to optimize bone development while preserving growth potential. Conversely, excessive doses should be avoided, as they may reduce final height due to premature epiphyseal closure.

Some studies have demonstrated that follicle-stimulating hormone (FSH) exerts direct effects on bone, independent of its reproductive role (57). Experimental studies in FSH- or FSH receptor-deficient mice have shown increased bone mass despite normal gonadal development (58), while administration of FSH promotes bone loss through both pro-resorptive and anti-anabolic mechanisms (59). FSH stimulates osteoclast differentiation and activity via specific FSH receptor isoforms, activating intracellular signalling pathways (ERK1/ERK2 and IκBα) and enhancing cytokine production, including RANK, IL-1β, TNFα, and IL-6, thereby amplifying bone resorption (60, 61, 62). Concurrently, FSH inhibits osteoblast differentiation, further impairing bone formation (59). In humans, elevated FSH levels, such as those observed in menopause or hypergonadotropic amenorrhoea (63, 64, 65), correlate with lower bone mineral density and higher bone turnover, whereas individuals with genetic variants reducing FSH receptor signalling show relative skeletal protection (66).

Considering all these findings, in conditions of primary hypogonadism characterized by chronically elevated FSH levels, the specific impact of FSH on bone metabolism remains to be fully elucidated. It is still uncertain whether oestrogen replacement during pubertal induction is sufficient to offset the potential adverse skeletal actions of FSH, or if additional strategies are required to mitigate its negative influence on bone.

As for psychosocial outcomes, pubertal induction likewise affects not only physical growth but also emotional and social development. It is known that puberty represents a transitional phase in which biological challenges intertwine with social and cognitive demand.

There is scant direct evidence quantifying psychological outcomes after pubertal induction with standardized scales and longitudinal follow-up. Data in the literature are mostly on congenital hypogonadotropic hypogonadism and TS and show that disrupted or delayed puberty carries psychosocial burden (67, 68), and timely, well-managed induction is advocated partly to mitigate these risks (69). Moreover, robust trials/cohorts with depression/anxiety/health-related quality of life, as primary endpoints are rare; most sources are reviews, observational cohorts, or patient surveys focusing on somatic outcomes, adherence, and satisfaction (69). This latter study examined experiences with pharmacological pubertal induction in girls and women with TS. Using a 15-item anonymous online survey shared via social media, 109 patients or caregivers provided information about oestrogen–progesterone replacement therapy. Most began treatment between ages 10 and 16, mainly with oral or transdermal oestradiol. Overall, 58.7% of respondents were satisfied with breast development, and later initiation of therapy was linked to lower satisfaction. Authors concluded that optimal management should aim to achieve desired developmental outcomes, minimize side effects, and meet patient expectations to encourage long-term adherence to treatment (69).

Future research should aim to further explore bone metabolism and psychosocial dimensions, with the goal of advancing and refining clinical practice in pubertal induction.

Conclusion

Pubertal induction should occur within a physiological timeframe to ensure coordinated growth, sexual maturation, psychological well-being, and resemblance to natural puberty.

Starting induction with a growth-promoting TD 17β-oestradiol dose, possibly through overnight-only exposure, may benefit patients at risk of reduced adult height. Gradual oestrogen escalation and appropriate timed progesterone introduction is crucial for optimal outcomes as early progestin use can hamper uterine growth and maturation.

However, the therapeutic approach should be individualized, considering patient-specific characteristics, clinical circumstances, and personal preferences. Future research should focus on bone metabolism and psychosocial outcomes, while also promoting equitable access to formulations specifically designed for children and adolescents, rather than extrapolated from adult treatments.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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