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Hypogonadism in adolescent girls: treatment and long-term effects

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Abstract. *Background and aim:* Hypogonadism in adolescent females presents as delayed puberty or primary amenorrhea. Constitutional delay of growth and puberty, hypogonadotropic hypogonadism and hypergonadotropic hypogonadism represent the principal differential diagnosis of delayed puberty. Girls with hypogonadism require hormone replacement therapy to initiate and sustain puberty. We aimed to provide a brief review concerning treatment for female adolescents with hypogonadism and further to focus on current data regarding long-term effects of therapy. *Methods:* The published studies and articles of the international literature were used regarding the approach to adolescent girls with hypogonadism. *Results:* The aim of therapy is the development of secondary sexual characteristics and achievement of target height, body composition and bone mass, to promote psychosexual health and, finally, to maximize the potential for fertility. Hypogonadal females need long-term HRT, so it is of great importance to fully define risks and benefits of therapy. *Conclusions*: The optimal pubertal induction in women contains both estrogens and progesterone regimens. Different therapeutic options have been described over the years in the literature, but larger randomized trials are required in order to define the ideal approach. The latest acquisitions in the field seem to propose that transdermal 17β-estradiol and micronized progesterone present the most physiological formulations available for this purpose. Further studies and follow up are needed concerning the long-term effects of HRT in adolescents. (www.actabiomedica.it)

Key words: Hypogonadism, adolescent girls, treatment, long-term effects

Background

Hypogonadism results from an impairment at any level of the hypothalamo-pituitary-gonadal axis (HPG axis). Primary gonadal failure is defined as hypergonadotropic hypogonadism (primary hypogonadism), whereas hypogonadotropic hypogonadism (secondary hypogonadism) indicates malformations within the hypothalamus or pituitary (1). Girls with either primary or secondary hypogonadism require sex steroid replacement therapy, including estrogen and progesterone replacement, to induce puberty (1). Pubertal induction aims to achieve secondary sexual characteristics, including breast and uterine development, growth spurt, peak bone mass, and psychological wellbeing (1). Several formulations have been used for the induction of puberty. The evidence is derived primarily from clinical experience, a few observational studies and controlled trials on small study populations (1-3). The available data so far indicates that transdermal 17β-estradiol and micronized progesterone have the most favorable outcomes and safety profile. However, randomized controlled trials are required to establish the best therapeutic approach. The lack of licensed hormonal medications in adolescence, results in off-label prescribing of preparations licensed for adults (1-3).

Puberty is initiated by the activation of the HPG axis. Hypothalamus begins to secrete gonadotropin-releasing hormone (GnRH) in a pulsatile way, and then GnRH stimulates pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, gonadotropins act at the level of the gonads, causing release of gonadal sex steroids (1). Pubertal timing varies across ethnicities and is influenced by genetic and environmental factors (1-3). Overall, 95% of females should initiate puberty between 8.5 and 13 years of age (1). The initial sign of puberty is breast budding (breast stage 2 on the Tanner scale). Menarche usually occurs 2–3 years after the onset of puberty, after peak height, which usually occurs between breast stage 3 and 4 (4). Hindrance in pubertal onset beyond the expected age (> 2-2.5 standard deviation values above the mean of the reference population), constitutes delayed puberty (DP) (3,5). Therefore, girls by 13 years of age without signs of breast development or without menstruation by 15 years of age or within 3 years of thelarche should be considered for evaluation (6).

In the framework of this study, we aimed to provide a brief review concerning treatment for female adolescents with hypogonadism and further to focus on current data regarding long-term effects of therapy.

Search methods

The published studies and articles of the international literature were used regarding the approach to adolescent girls with hypogonadism. A Medline / PubMed, Google Scholar database, as well as online portals search was conducted. Hypogonadism, adolescent girls, treatment and long-term effects represent the key words used for this review.

General principles

Etiology of hypogonadism

Hypogonadism can be either primary (hypergonadotropic hypogonadism) or secondary (hypogonadotropic hypogonadism). It is crucial to differentiate between constitutional delay of growth and puberty (CDGP) and permanent hypogonadism. Up to 30–56% of girls with pubertal delay is contributed to CDGP, currently the commonest cause of delayed puberty in girls (1,7,8). CDGP is considered an extreme variant of normal pubertal timing and is be diagnosed only by exclusion of other possible underlying causes (5). Treatment of CDGP involves expectant observation or short courses (3-6 months) of low dose sex steroid supplementation (1).

Hypogonadotropic hypogonadism is caused by disorders of the hypothalamus or pituitary, and it can be either congenital or acquired. In hypogonadotropic hypogonadism, GnRH or/and gonadotropins (FSH, LH) are either deficient or inactive, leading to decreased secretion of gonadal sex steroids. Congenital hypogonadotropic hypogonadism (CHH) is a genetic disorder affecting approximately 10-20% of adolescent girls with pubertal delay (7,8). Pathophysiologically, it regards GnRH deficiency, either due to developmental defects in the GnRH neuron migration or the GnRH neuronal network maturation (3,9), When CHH is associated with an absent sense of smell, commonly is termed Kallmann syndrome (1,3). CHH phenotypical manifestations may range from partial hypogonadism to complete hypogonadotropic hypogonadism, with patients presenting with normal or arrested pubertal development, secondary amenorrhea, or reversible hypogonadotropic hypogonadism (1,3,10). Several genetic syndromes are also associated with hypogonadotropic hypogonadism, namely CHARGE syndrome, Waardenburg syndrome, Prader–Willi, Laurence–Moon syndrome, Gordon Holmes syndrome, Bardet–Biedl syndrome, among others. Most patients undergo incomplete pubertal development with lack of pubertal growth spurt and underdeveloped genitalia, while other pituitary hormone deficiencies are often present (11).

The acquired causes of hypogonadotropic hypogonadism are due to structural or functional abnormalities of the hypothalamic-pituitary axis. Their etiology includes: central nervous system tumors (astrocytoma, craniopharyngioma, germinoma) or pituitary tumors, infiltrative diseases, infection, brain/pituitary irradiation, surgery or trauma, pituitary apoplexy, CNS ischemia, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy) and functional

deficiency (11). These conditions are often associated with hypopituitarism, a term used to describe deficiency in multiple pituitary hormones (12,13). Functional deficiency of the HPG axis is found in approximately 20% of girls with delayed puberty or incomplete pubertal development (1,8). The underlying pathophysiology is delay in the HPG axis maturation, secondary to chronic disease (e.g., anorexia nervosa, chronic renal disease, inflammatory bowel disease, sickle cell anemia and thalassemia, celiac disease, hypothyroidism and hyperprolactinemia, diabetes mellitus, cystic fibrosis), malnourishment, psychological or emotional stress, strenuous exercise (14). In this case, treatment should restore HPG axis function, addressing the underlying pathogenetic mechanism, including nutrition optimization, behavioral therapy, physical activity control and management of the chronic disease (14).

Failure in the ovarian hormone production leads to a block of negative hypothalamic–pituitary feedback and elevated gonadotropin levels, resulting in hypergonadotropic hypogonadism**.** Primary ovarian insufficiency (POI) is most often associated with chromosomal aberrations (for example Turner syndrome) or iatrogenic causes (chemotherapy or irradiation therapy) (15,16). Other less common etiologies include ovarian autoimmunity, infections, pelvic surgery and single mutations in genes involved in gonadal development (leading to ovarian dysgenesis) or ovarian estrogen production such as FSHR mutations and mutations in steroidogenic enzymes (e.g., CYP17A1 mutation leading to congenital adrenal hyperplasia) (17,18). Turner syndrome (TS) is the most common non-iatrogenic cause of POI in adolescents (15,16), affecting approximately 50/100.000 women (19,20).

Puberty induction in girls

Initially, it is essential to define the underlying cause of DP in order to initiate a tailored program of care, guided by a multidisciplinary team. Treatable causes (e.g., surgery or irradiation for the tumor, drug treatment of infective or chronic disease) of hypogonadism should be ruled out before starting puberty induction. Differential diagnosis should take into account CDGP and maturational delay in the HPG axis secondary to an underlying non-reproductive pathology, as mentioned earlier and in this case, a "wait-and-see" approach would be recommended. Additionally, in case of DP associated with functional hypogonadotropic hypogonadism, the initial consideration should be to address the underlying cause of HPG axis disorder, aiming to restore its optimal functionality. A specific therapeutic approach is needed on the other hand in pathological cases of DP. In the absence of definitive diagnosis, treatment may be initiated and retested at a later time (4,21).

Estrogens are recommended for puberty induction in girls. Natural human estrogens (estradiol/17β-estradiol E2) are the dominant formulations currently used and are preferred to the non-natural alternatives (e.g., ethinylestradiol, conjugated equine estrogens). The optimal type, route of administration and dose of estrogens used for puberty initiation are not well established. So far, no clear advantage has been found for any type of hormone treatment to initiate or sustain puberty in girls (21).

A universal consensus on the ideal age to begin treatment in patients with known hypogonadism does not yet exist and recommendations rely on data regarding the average age of onset of puberty and possible uterine and bone risks of a delay. The age of 11-12 years (4,21,22) is considered appropriate in girls who do not show signs of puberty and have confirmed hypogonadism after testing. When diagnosis is unclear or a simple delay in puberty is suspected, treatment may be postponed to allow time for diagnosis or permit more time for continuous growth (4,21,22). However, in order to achieve a normal hormonal status and mitigate adverse outcomes of delayed onset of puberty, pubertal induction should be initiated no later than 13-14 years in females (4,21,22).

Estrogen therapy is usually initiated at low doses, as to imitate normal puberty and preserve growth potential, with increases in dosing at 6-month intervals. There remain currently many uncertainties regarding the optimal pubertal induction regimen (21). The starting dose is theoretically approximately 10% of adult dosing (23) or one-eighth to one-quarter (24) of the adult dose depending on the regimen, and is gradually increased every 6-12 months over a 2-3-year period, until an adult dose is reached (23,24). Doses can then be modified to the response (Tanner stage, bone

age, and uterine growth), and if available, by measuring estradiol levels with an ultrasensitive assay (25). However, no studies were found comparing titration or adjustment of hormonal therapy for puberty induction based on puberty progression, and additionally no studies to date have studied outcomes in relation to the rate of dose increase for the different preparations and the different diagnoses (21). Estrogen dosing can progress more promptly in cases where hypogonadism is diagnosed later or develops after initial normal pubertal progression (4).

In case of episodes of prominent breakthrough bleeding or after 24-36 months of estrogen therapy to establish menstrual cycles, a progestin is required to be added, in order to prevent endometrial hypertrophy. It is also added to minimize the risk of endometrial cancer (4,21,22,24,26).

Further clarifications are worth mentioning in relation to the management of patients with TS, where HRT should be optimized for linear growth. Growth hormone therapy is a standard treatment in girls with TS and short stature. Therefore, if growth potential exists, estrogen replacement may be started later or dose increased more slowly, to allow for a long period of other growth promoting approaches to act (11,21).

Treatment approaches

Estrogen replacement therapy

Several types of compounds and routes of administration of estrogens are available. There have been numerous studies presenting schemes of estrogen replacement therapy (ERT) for pubertal induction. ERT has been mainly studied in postmenopausal and adult women and any application of these findings to adolescent females can only be extrapolated Pediatricians have at their disposal estrogen formulations aimed for use by adult women, which they use off-label, as there are no licensed hormone preparations for pubertal induction (4,21). In young girls with hypogonadism, the clinical results using different estrogen formulations are derived from small studies or trials, while most regard patients with Turner syndrome (TS) (4,21).

Different formulations of estrogens available are: oral or transdermal (patch or gel) 17β-estradiol (the most physiological form of estrogen), oral ethinylestradiol (synthetic form of estrogen), and conjugated equine estrogens (xenoestrogen) (27,28,29). Published data regarding the clinical efficacy of oral ethinylestradiol (EE) in pubertal induction are limited (22), and data regarding conjugated equine estrogens (CEE) suggest increased cardiovascular risks; therefore, they should be avoided (27-29). Developing data reveal greater safety and efficacy associated with 17β-estradiol (17β-E2) compared with EE or CEE to induce puberty (30-38). Transdermal estradiol offers a more physiological route of delivery in the absence of the first-pass effect through the liver; thereby leading to lower hepatic metabolism and stable state profiles, with lower peak serum 17β-E2 concentrations than the oral route, and also avoiding the accumulation of non-physiologic estrogens (39,40). Moreover, the oral route is linked with a pro-coagulable state (41) and elevated danger of stroke in postmenopausal women (42). Of note, some studies demonstrated that treatment with 17β-E2, especially in the transdermal form, resulted in more effective feminization, faster bone accrual at the spine, and increased uterine growth compared with CEE regimens (43,44). In addition, measuring estrogen levels is feasible during treatment with 17β-E2, but cannot be performed dependably for CEE and is not available for EE (30).

Transdermal estradiol is usually used in pubertal induction in the form of a patch, cut up to deliver the desired dose of 17 β-E2, and easily adjustable (21). The transdermal gel form of 17 β-E 2 gel is not used for the induction of puberty, due to lack of literature data and proper dosage adjustment (45). Regarding estradiol valerate, clinical data is currently limited and other forms of estradiol, namely vaginal rings, are not suitable for girls of this age (30).

Estrogen administration should be initiated at low doses with the aim of mimicking estradiol levels in early puberty, and then doses are gradually increased with intervals of 6-12 months over a period of 2-3 years (28). One of the most widely used induction regimen is that proposed by Davenport (38), consisting of low transdermal estradiol doses, initially overnight, for 18 to 24 months (starting from 0.1μg/kg to doubling

every 6 months) considering body weight and gradually adjusting the patch size until target estradiol levels are reached. According to another proposed regimen by Ankarberg et al. (25) for the initiation of estrogen treatment with nocturnally administered E2 patches, the starting doses can be 0.05–0.07 μg/kg, in order to mimic E2 levels during gonadarche. In older cases, when breast development is of high priority, the initiating dose can be 0.08–0.12 μg/kg. One recent study (46) investigated faster protocols of puberty induction for girls with TS, particularly in cases of delayed diagnosis, consisting of initially 12.5μg/24h for the first two months, followed by 25.0μg/24h until breakthrough bleeding. The study found acceptable pubertal progression, no effect on the potential of growth and adequate uterine volume increase, not correlated to the dose or duration of treatment (46). Finally, a more simplified regimen (47) proposes initiation of therapy with one-quarter of a 25-μg patch and slow increase of the dosage to adult levels over 2-2.5 years, while another proposal applies the same dose midweek (22). Delemarre et al. (48) have proposed an oral 17β-E2 regimen, starting with 5 μg/kg of oral 17β-E2 per day, doubling every 6 months until an adult dose of 2 mg per day is reached in 2 years. Another study (49) suggests that a dose of 0.2 mg/day for the first year, followed by 0.5 mg/day the second year was not inferior to weight dependent dosage regimes. Recently, Zacharin et al. (37), targeting at a simple administration, propose initial dosage of 0.5 mg every other day for 3 months, followed by 0.5 mg a day for 6-9 months, 1 mg/day for one year, then reaching the adult dose of 2 mg/day.

It is worth noting that puberty induction regimen (route, drug and dose increments) should be personalized for each girl, taking into consideration the patient and their family and considering other parameters, namely age, height and growth potential, pubertal stage or concomitant conditions. Treatment should be also individualized according to the rate of physical changes (4,21,22,30).

Progesterone replacement therapy

Progestins are typically introduced after a 2-3 years duration of estrogen treatment or if more than one episode of remarkable breakthrough bleeding occurs, on the condition that optimal breast and uterine maturation has been achieved (21,22). The combined hormone therapy of estrogen and progestin should not be administered before the completion of puberty which includes full development of secondary sexual characteristics (21). Progestins are required to induce menstrual cycles, to minimize irregular bleeding and prevent endometrial hyperplasia as well as endometrial cancer (4,21,22,30). However, there is a lack of valuable data regarding the optimal progestin induction scheme (21). Each progestin formulation exerts unique effects, related to their affinity for progesterone or mineral/glucocorticoid or androgen receptors (50). Options for treatment mainly include natural micronized progesterone (100–200 mg once daily) and synthetic progesterones such as oral medroxyprogesterone acetate (MPA) (5–10 mg daily), norethisterone acetate (1 mg daily), and dydrogesterone (10 mg daily) (22,51). Generally, non-androgenic progestins appear to be a more suitable choice since they pose lower metabolic and cardiovascular risks (52). Micronized progesterone offers good cycle control, while appears to be safer than MPA in current literature, regarding the risk of breast cancer, the effect on metabolism, the incidence of thromoboembolic events (53,54). Norethisterone acetate is not advisable for younger girls, since it has the most androgenic effects, while dydrogesterone is not widely available as a standalone preparation, outside HRT combinations. Taking these into consideration, most authors consent to the recommendation of micronized progesterone (9,38,55). Progesterone is usually given for 12 -14 days during the last two weeks of the menstrual cycle with the frequency of at least every 2-3 months to prevent endometrial hypertrophy (4). In clinical practice, doctors should choose between a combined-sequential and combined-continuous regimen of administration (4). In case of combined-sequential regimen, estrogen is administered for 21-28 days per month and the progestin for 10-14 days per month. In case of combined-continuous regimen, estrogen formulations are administered continuously (4). Combined oral contraceptives containing an estrogen and a progestin may be used as HRT, only in post-pubertal hypogonadal females, taking into consideration their adverse cardiovascular and metabolic profile, as well as the increased risk of hypertension and venous thromboembolism (56).

Patients' follow-up and life-long replacement therapy

Response to hormone replacement therapy should be monitored by assessment of development of secondary sex characteristics, linear growth, uterine volume and bone density (22). Monitoring blood concentrations of estradiol after treatment initiation and dose changes, ideally with an ultrasensitive assay, is a useful complementary tool for evaluating compliance and aiding in treatment titration (29). However, estradiol levels for optimal linear growth, bone health and uterine health have not yet been determined (4,20,21,29).

At the beginning of pubertal induction and at the end of treatment, uterine size and shape should be monitored using pelvic ultrasound in order to document endometrial thickness and optimize the timing for progestin initiation (29). Screening for thromboembolic risk is recommended only in girls with a personal or family history (54). As for bone mineral density (BMD) monitoring, it is usually investigated at baseline and upon completion of pubertal induction, in patients with risk factors for low BMD (56). In the event of low values, reassessment within 3 to 5 years is performed (30). Periodically a metabolic profile should be also investigated (22). It is recommended to change pubertal induction treatment to permanent adult sex hormone replacement therapy at the end of puberty (4) and continue ERT until the average age of menopause (around 52 years of age) (4).

Long-term effects of sex steroid replacement therapy in females with hypogonadism

Although benefits and risks of sex steroid replacement therapy have been broadly studied in postmenopausal and adult women, further studies are required to define the long-term effects of puberty induction in girls with hypogonadism (21). In the scope of this review, we will mainly discuss the effects of HRT on growth, feminization, bone mass and bone mineral density as well as cardiovascular and metabolic risk profile of HRT.

HRT does not interfere with growth and permits the achievement of adult height (30). Particularly, low-dose estrogen regimens used to initiate puberty appear to promote growth and preserve growth potential (21). However, physicians should keep in mind that early high doses of estrogen or rapidly increased dosage could lead to reduced final height (22). Regarding the effects of estrogen therapy on insulin growth like factor-1 (IGF1) (which plays a crucial role along with growth hormone in linear growth in children), there doesn't appear to exist a clear consensus in the literature (30). Transdermal 17β-estradiol has no effect on hepatic metabolism; hence it does not lower insulin-like growth factor (IGF)-1 levels (58), possibly enhancing longitudinal growth, however this remains to be confirmed (22). Oral ethinylestradiol, on the other hand, has a first-pass hepatic effect and is therefore associated with lower IGF-1 concentrations. (22). Mauras et al. (59), who tested the effects of oral versus transdermal estrogen on growth hormone-treated girls with TS, showed no clinically significant change in IGF-1 concentrations after either form of estrogen. The authors illustrate the fact that the route of 17β-E2 administration does not seem to have a significant impact on IGF-1 concentrations. On the contrary, Torres-Santiago et al. (39) showed lower IGF-1 values in the oral group.

Regarding the effects of HRT on the development of secondary sexual characteristics, the outcomes of almost all regimens appear to be encouraging with the achievement of breast stage 2 on Tanner scale during the first 6 months, and stage 4 after approximately 2 years, similar to spontaneous puberty (46,55). Conversely, data on uterine maturation are not equally reassuring. Uterine volume appears to be influenced by route of administration, dosage, age at initiation, as well as duration of treatment (44,60-65). A recent study (66) in hypogonadal women who underwent pubertal induction, found that uterine growth is frequently compromised, even with standard estrogen therapy. Another work indicated that, higher oral 17β-estradiol dose for 5 years, in the years immediately after pubertal induction, led to more girls with TS achieving a normal uterine size (61). Uterine development has also been reported worse, in patients treated with non-physiological estrogen and progestin formulations (60).

Achievement of bone health is one of the major concerns during estrogen therapy. Research shows that

the highest rate of bone mass accrual occurs 1 year prior to menarche and after the first 3 years of menarche (67). Primary ovarian insufficiency negatively affects bone health; therefore, timely estrogen replacement is considered necessary to reduce the risk of osteopenia or osteoporosis (68). Regarding the effects on bone mass and density between different estrogen preparations, Torres-Santiago et al. found significant but similar improvements in whole-body and lumbar bone mineral density over 12 months in girls with Turner syndrome, in either oral or transdermal 17β-estradiol (39). Transdermal estradiol compared with conjugated oral estrogens resulted in faster spinal bone accrual (44). Fewer studies have assessed the effect of ethinylestradiol on bone mass accrual. Two randomized crossover trials have indicated less favorable effects of ethinylestradiol on increasing bone mass and bone turn-over (69,70).

There are concerns regarding the systemic and hepatic effects of oral estrogens, as administration of any oral estrogen exposes the liver to high concentrations (21). On the contrary, transdermal 17β-estradiol bypasses first pass effect, having no hepatic effect (4,21,22,30). Regardless, no harmful effects have been reported so far even with oral estrogens (21). In parallel, metabolic effects of transdermal and oral routes of estrogen delivery are similar concerning lipid metabolism, glucose metabolism, insulin tolerance, protein turnover (59,71,72,73).

It is known that estrogen deficiency is associated with an increased risk of cardiovascular disease (21,22). A study by Kalantaridou et al. (74) demonstrated that young women with POI have significant vascular endothelial dysfunction that may contribute to increased risk of cardiovascular disease and mortality. In the same study, hormone therapy restored endothelial function within 6 months of treatment. Moreover, another study showed that HRT results in decreased blood pressure, improved renal function, and lowered activation of the renin-angiotensin system in young women with POI (75). In a systematic review and meta-analysis, a more favorable impact of transdermal estrogens, compared with oral estrogens was found on certain markers of cardiovascular risk, including fasting glucose, total cholesterol and triglyceride concentrations (76).

As already mentioned above, administration of oral estrogen exposes the liver to supraphysiologic levels, resulting in an increase in procoagulation factors (77). This may explain the greater thromboembolic risk of oral versus transdermal estrogen, supported by numerous studies (41,42,78-83), especially in women with other existing risk factors such as obesity (79).

Regarding progestins, their beneficial role consists of inducing menstrual cycles and preventing endometrial pathologies (4,21,22,30). Progesterone, nortestosterone and pregnane derivatives do not present an increased risk of stroke, while the same is not true for nonpregnane derivatives (41, 42, 78).

It is important to mention that in TS, the long-term risk of breast cancer after prolonged oral or transdermal estrogen remains much lower than among control women (84).

Finally, pubertal induction appears to promote psychosexual development and to prevent psychological consequences of delayed puberty with decreased self-esteem, social withdrawal, anxiety as well as sexual inactivity in later life (30).

Conclusions

Pubertal induction in adolescent girls with hypogonadism is crucial for effective feminization, psychosexual development, achievement of peak bone mass and future fertility. Pubertal induction should be achieved within a physiological timeframe to obtain a normal endocrine milieu. Several different puberty induction regimens exist, but larger randomized clinical trials are required to ensure the best therapeutic approach. According to current literature, transdermal 17β-estradiol is considered the first choice, starting with low doses and increasing every 6-12 months on the basis of response. A progestin should be added when bleeding occurs or after 2-3 years of estrogen treatment. So far, micronized progesterone has shown the most effective and safe profile. Hypogonadal females need long-term HRT, so it is of great importance to fully define risks and benefits of therapy concerning growth, breast and uterine development, bone health, cardiovascular and metabolic effects, as well as psychosexual health. Physicians should bear in mind that the

risks of not treating offset the risks of treatment, in most cases of hypogonadism. Further studies and follow up are needed concerning the long-term effects of HRT in adolescents.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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