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Timing and regimen of puberty induction in children with hypogonadism: a survey on the practice in Arab countries

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Abstract

Objectives: There are some variations in the practice of puberty induction between different regions; however, data from Arab countries are lacking. We aimed to survey the practice of pediatric endocrinologists in Arab countries on the timing and regimen for puberty induction in girls and boys with hypogonadism.

Methods: An online questionnaire was emailed to physicians registered in the Arab Society for Paediatric Endocrinology and Diabetes.

Results: In total, 106 replies from 17 countries were received. In non Turner syndrome (TS) girls, puberty was induced by 49.4% of participants at 12–13 years and by 32.5% at ≥ 14 years. Ethinyl estradiol and conjugated estrogen were the most popular preparations used (29.7 and 16.6%, respectively). Of the participants, 60% introduce progesterone either at 2–3 years after starting estrogen or following a significant breakthrough bleeding on estrogen. In girls with TS, 84.2% of participants prescribed estrogen to those aged 11 years and older (51.5% at 11–12 years) and 5.3% prescribed it to those at the prepubertal age. In boys, 57.3% of participants induce at ≥ 14 years, 80.6% use intramuscular testosterone and 46.5% start with 50 mg/kg/month. Human chorionic gonadotropin is more used in non-Gulf Arab countries (18.2 vs. 2.9%; p 0.036) with a

trend of using oral testosterone undecanoate in Gulf states (12.2 vs. 2.0%; p 0.051).

Conclusions: We describe the approach to puberty induction in boys and girls among pediatric endocrinologists in Arab countries. The observed variation in practice would be useful in developing regional consensus guidelines on puberty induction in children with hypogonadism.

Keywords: Arabs; ASPED; hypogonadism; puberty.

Introduction

Hypogonadism can be caused by primary gonadal dysfunction (hypergonadotropic) or secondary to impaired gonadotrophin secretion/action (hypogonadotropic). Both forms can be congenital or acquired and manifest from birth until pubertal age. The majority of these patients will ultimately need induction of puberty to achieve optimal final height and bone mass, alleviate the psychological stress and provide opportunity for future fertility [1].

The ideal regimen for puberty induction should mimic the pubertal physiology; however, there are various challenges to achieve this target. First, the ages of starting and finishing puberty are not well defined. Although it is traditionally accepted that the absence of puberty signs by the age of 13 in girls and 14 in boys is considered as delayed puberty [1, 2], there are racial and ethnic variations in the onset and tempo of puberty [2–5]. Second, most available agents for puberty induction need careful titration because they have different pharmacodynamics and kinetics compared to endogenous sex steroids, and their impact on growth is unpredictable [6, 7]. Third, up to 10% of individuals with hypogonadism can recover following the exposure to puberty induction agents [8–10].

Currently, there are no clear guidelines on the optimal timing and regimen of puberty induction [6, 7]. To the best of our knowledge, only two surveys on the practice of puberty induction were published. Drobac et al. [11] explored the views of US pediatric endocrinologists of inducing puberty in both genders while Kiess et al. [12] surveyed the European practice in girls. Although the induction age in girls was similar, most pediatric endocrinologists in the

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USA used conjugated estrogen, while ethinyl estradiol was the popular choice in Europe [12]. The lack of similar data from Arab countries triggered the Arab Society for Paediatric Endocrinology and Diabetes (ASPED) to survey the starting age and regimen for puberty induction in boys and girls with hypogonadism among its members.

Materials and methods

Study design

This survey was conducted between July and October 2019 using the software *surveyMonkey.com* (team advantage). An invitation, with a link to the online questionnaire, and three reminders were emailed to pediatric endocrinologists registered in the ASPED database. The invitation outlined the purpose of the study, the voluntary nature of contribution, the unconditional right to decline participation and opting out from the database. Strict confidentiality of participants' details was ensured, and data were collected anonymously. Because of the heterogeneity of the participants, two comparisons were made. One between the fully trained consultants and trainees and the other between physicians practicing in Gulf states and those in other Arab countries. The six Gulf states (Bahrain, Kuwait, Oman, Saudi Arabia, Qatar and United Arab Emirates) are classified by the world bank among the high-income countries while other Arab countries are in the intermediate- or low-income groups (www.datahelpdesk.worldbank.org, accessed May 2020). The study was approved by the ASPED board, but formal ethics committee approval was not deemed necessary for such a quality assurance type of survey.

The questionnaire

A comprehensive literature search on the subject was undertaken by the coauthors. A questionnaire was drafted based on debatable areas related to the starting age and preparations used for puberty induction in boys and girls. A hard copy of the questionnaire was piloted during the fifth ASPED- ESPE (European Society for Paediatric Endocrinology) school in 2018 [13], and the comments of the school participants (12 consultants and 41 trainees) were considered in the final version of the questionnaire which was approved by all coauthors. The first five questions covered respondents' demographics including country of practice and professional level while the sixth one assessed the annual number of patients with delayed puberty managed by the practitioner. The remaining 10 questions inquired specifically about the timing, dose and preparation used for induction and maintenance in boys and girls. A specific question was asked on the age of starting estrogen in girls with Turner syndrome (TS).

Results

Of the 273 physicians who opened the invitation email, 106 filled in the questionnaire giving a response rate of 38.8%. These physicians were practicing in 17 Arab countries

(47.1% in Gulf states) with the highest response rate from Oman (18%), followed by Saudi Arabia (16%) and Iraq (13%). The number of responders per each country is illustrated in Figure 1. Two responders were excluded because they only answered the demographic questions. Of the remaining 104 responders, 63 (60.5%) were fully trained consultants, 94 (90.4%) were practicing in government hospitals and 65% managed more than five patients with delayed puberty annually. Seventy-two of the 104 responders (69%) completed the whole questionnaire while the remaining skipped 1–2 questions. The average reply to the 10 questions was 83 of 104 (80%).

Puberty induction in girls

In girls with TS, 84.2% of participants would start estrogen at 11 years and older, with 11–12 years being the most frequently selected age group (51.5%), while 5.3% of participants would consider early/mid childhood (4–7 years) start (Figure 2). In non-TS girls, puberty was induced by 49.4% of physicians, at 12- to 13-year-olds, while 32% of them did so at ≥ 14 years old (Figure 3). There was no significant difference in the age of inducing puberty between consultants and trainees, neither between responders of Gulf states and other Arab countries. The replies to questions related to the estrogen preparations and the timing of progesterone and preparations are summarized in Table 1. Ethinyl estradiol and conjugated estrogen were the most popular preparations to induce puberty selected by 29.7 and 16.6%, respectively, while esterified estrogen was preferred by 20% of trainees compared to 3.3% by consultants ($p = 0.008$). Apart from three trainees, all participants who answered this question add progesterone, with 60.5% would do so either following a significant breakthrough bleeding on estrogen (33.3%) or 2–3 years after starting estrogen (26.7%). Of the progesterone preparations, oral contraceptive pills were the most popular choice (42.3%) followed by medroxyprogesterone acetate (19.2%).

Puberty induction in boys

Puberty was induced by most participants (57.34%) at the age of 14 years and older, while 34.1% did so at the age between 12 to 13 years (Figure 4). The answers to questions related to the androgen preparations and regimen for puberty induction in boys are summarized in Table 2. Testosterone was used to induce puberty by 79%, and 52% used it for maintenance. Most participants (80.6%) preferred intramuscular (IM) testosterone (70.9% sustanon). When asked

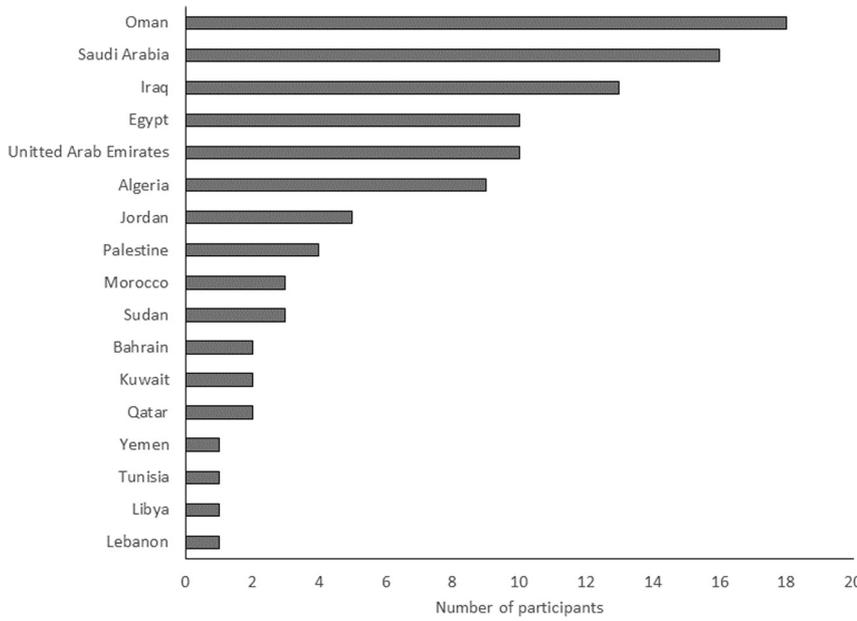


Figure 1: The number of responders per country of practice.

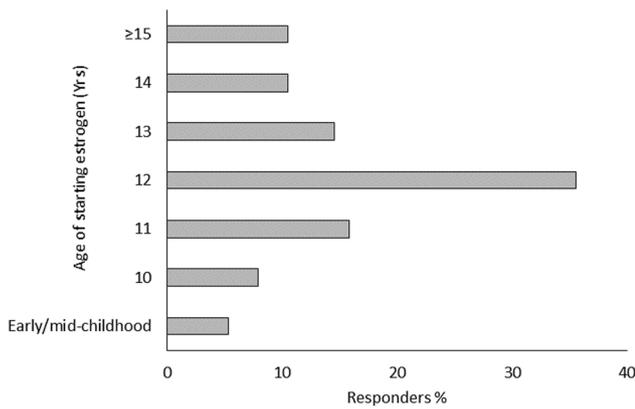


Figure 2: Age at starting estrogen therapy in girls with Turner syndrome used by the Arab pediatric endocrinologists (%). Early/mid-childhood is the age between four and seven years.

about the starting dose of IM testosterone, 46.5% used 50 mg monthly, 32.5% used 25 mg and 13.9% used 75 mg. There was no significant difference in the replies between the consultant and trainees in puberty induction for boys. There was no significant difference in the practice between the Gulf states and other Arab countries apart from more use of human chorionic gonadotropin (HCG) for induction in non-Gulf countries (18.2 vs. 2.9%; p 0.036) and a trend of using oral testosterone undecanoate in Gulf states (12/2 vs. 2%; p 0.051).

Discussion

We report the first data on the practice of puberty induction in boys and girls with hypogonadism in Arab countries.

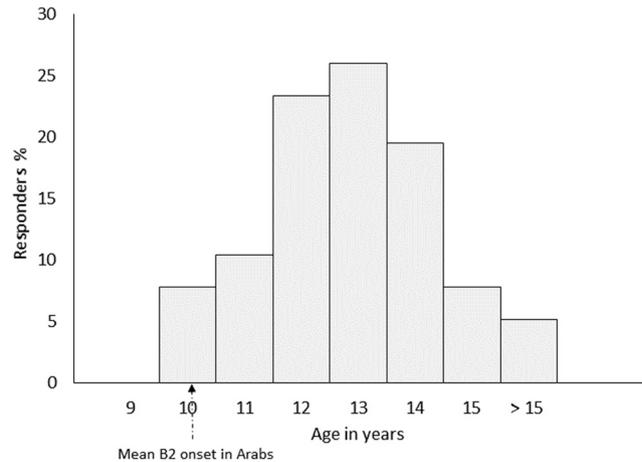


Figure 3: Answers of Arab endocrinologists (%) to the question of the chronological age for puberty induction in girls with hypogonadism and Turner syndrome. The dotted arrow on the horizontal axis points to the mean age of puberty onset in an Arab population [3].

Beside the interest in the subject, the electronic nature of the survey allowed more than 100 clinicians from 17 countries to take part, and the multiple reminders raised the response rate to 38.8%, which is higher than a rate of 28% reported from a US workshop-based survey on the same topic [11]. To the best of our knowledge, this is the first survey to address the time of introducing progesterone in hypogonadal girls without TS and the starting dose of testosterone in hypogonadal boys. There was some variation in the practice of our participants with no significant differences in the replies between consultants and trainees. We suspect that the observed variation may reflect different

Table 1: Regimen of puberty induction in girls.

Which estrogen preparation would you use to induce puberty?	
Responders = 91	
Depot estradiol	6 (6.6%)
Transdermal patches	16 (17.6%)
Estradiol gel	2 (2.2%)
Oral: conjugated estrogen	15 (16.5%)
Oral: ethinyl estradiol	27 (29.7%)
Oral: 17 β estradiol	9 (9.9%)
Oral: esterified estrogen tablets	8 (8.8%)
Other estrogen preparation	2 (2.2%)
Combined pills	6 (6.6%)
When would you add progesterone during puberty induction in girls?	
Responders = 71	
Six months after starting estrogen	12 (16.9%)
12 months after starting estrogen	13 (18.3%)
2–3 years after starting estrogen	19 (26.7%)
Presence of a significant breakthrough bleeding on estrogen treatment	24 (33.8%)
Never add progesterone	3 (4.2%)
Which of the following progesterone forms would you use?	
Responders = 78	
Oral: norethisterone	18 (23.1%)
Oral: utrogestan	3 (3.8%)
Medroxyprogesterone acetate	15 (19.2%)
Combined patches (E+P)	9 (11.5%)
Standard oral contraceptive pills	33 (42.3%)

local protocols, health-care system and training backgrounds.

Almost half of our participants induce puberty in non-TS hypogonadal girls at chronological age of 12 to less than 14 years and 31% of them did so at the age of 14 years and above. This practice is similar to the one reported in the 2004 US survey [11]. When replies were analyzed according to a cutoff age of ≥ 13 years, used in the European survey by Kiess et al. [12], a similar practice was observed with 45.5% of Arabs initiating therapy between 13 and <15 years compared to 47.9% in Europe [12]. Interestingly, 13% of our responders would wait until after the age of 15 years to induce puberty. It is possible that the practice of late induction among some Arab clinicians reflects patients' or parents' preference due to cultural resistance to "hormone" therapy; however, a survey on patients' and parents' attitude on puberty induction in Arab countries is needed to explore this issue.

Our survey is the first to address the timing of adding progesterone in hypogonadal girls without TS. In agreement with different expert opinions [6, 7, 14, 15], all participants who answered this question, except three trainees, agreed to add progesterone with 60.5% doing so either following a significant breakthrough bleeding on

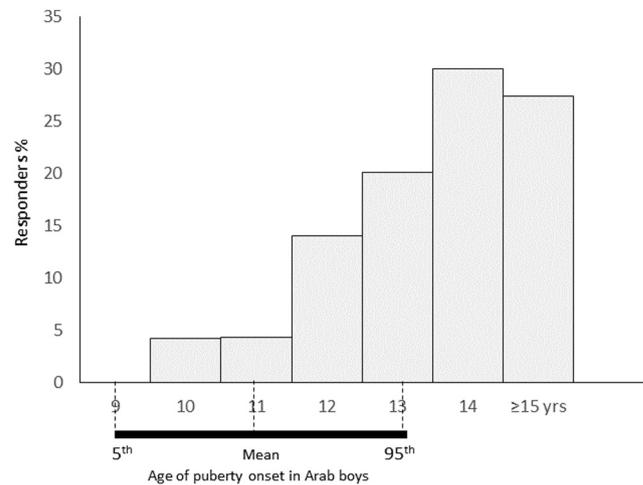


Figure 4: Answers of Arab endocrinologists (%) to the question of the chronological age for inducing puberty in boys with hypogonadism. The mean age with fifth and 95th percentiles of puberty onset in an Arab population [4] is illustrated on the horizontal axis.

estrogen (33.3%) or 2–3 years after starting estrogen (26.7%). Despite the lower side effects and the advantage of progesterone preparations in providing better titration of progesterone dose, oral contraceptive pills were the most popular choice by Arab physicians (42.3%) followed by medroxyprogesterone acetate (19.2%). This selection could be related to the easier availability of oral contraceptive in Arab countries and the familiarity with its use and side effects. It is also possible that it may reflect patients' preference of the practicality of using combined pills instead of two medications.

The age of estrogen induction in girls with TS has been the subject of ongoing debate. The current consensus is that if gonadotropins are elevated, treatment should begin at 11–12 years to mimic normal physical and social development without interfering with the effect of growth hormone therapy on final height [16, 17]. Although some studies showed the benefits of prepubertal introduction of low-dose estrogen on lipid and metabolic profile and denied its negative impact on final height [18, 19], this practice is still under investigation [16]. In this survey, 84.5% would start estrogen for girls aged 11 years and older with TS, with 11–12 years being the most frequently (51.3%) suggested age, while only 5.3% consider it during early/mid childhood. This is in line with a recent clinical practice guideline for the care of girls and women with TS [16] and comparable to a recent Turkish survey [17] in which almost 40% started estrogen treatment at the age of 12–13 years.

Oral ethinyl estradiol was the most common form of estrogen prescribed by Arab physicians (29.7%) which was

Table 2: Regimen of puberty induction in boys.

Of the following agents, which is your first choice to induce puberty in boys? Responders = 81	
Human chorionic gonadotropin (HCG)	10 (12.3%)
Pulsatile gonadotropin	7 (8.64%)
Testosterone	64 (79.01%)
If testosterone is selected, which of the following preparation would you use? Responders = 93	
Buccal tablets: slow release	0
Oral: testosterone undecanoate	6 (6.4%)
Cream: testosterone cream 5%	3 (3.22%)
Gel: dihydrotestosterone	3 (3.22%)
Transdermal gel: testosterone 1, 2%	2 (2.15%)
Transdermal testosterone patch	2 (2.15%)
IM testosterone (Sustanon)	66 (70.9%)
Testosterone depot (Nebido/Reandron)	9 (9.7%)
Other (please specify) ^a	2 (2.15%)
If testosterone used for induction, which preparation would you use for maintenance? Responders = 93	
Oral: testosterone undecanoate	8 (8.6%)
Buccal tablets: slow release	2 (2.2%)
Cream: testosterone cream 5%	1 (1.1%)
Gel: dihydrotestosterone	2 (2.2%)
Transdermal gel: testosterone 1, 2%	6 (6.5%)
Transdermal testosterone patch	6 (6.5%)
Intramuscular testosterone (Sustanon)	49 (52.6%)
Testosterone depot (Nebido/Reandron)	17 (18.3%)
Other (please specify) ^b	2 (2.2%)
When using intramuscular testosterone for pubertal induction, what is the starting dose? Responders = 86	
25 mg/month	28 (32.5%)
50 mg/month	40 (46.5%)
75 mg/month	6 (6.9%)
>75 mg/month	6 (6.9%)
Less than 25 mg/month	2 (2.3%)
Other dose/frequency (specify) ^c	4 (4.6%)

IM, intramuscular.

^aA responder thought the choice is depending on the child. Another responder suggested testosterone enanthate.

^bOne ticked the option but left it blank and another wrote "Transdermal testosterone is not available"

^cOne suggestion was to induce puberty by 125 mg/month, another was 25 mg/month which is already provided option and other stated that lack of knowledge and other thought it relates to the underlying condition.

similar to the European survey [12] but different from the US practice where conjugated estrogen was the most popular one [11]. However, the European and the US surveys were conducted long time ago and the practice might be influenced by market availability at that time. Interestingly, despite of being more physiological, the use of estradiol patches in our surveys was not high (11.5%) which may reflect the availability. Esterified estrogen is not easily available in Arab countries; however, it was selected by 20% of trainees compared to 3% of the consultants, which

could reflect opinions rather than practice. Various explanations have been suggested for the variations in the selection of estrogen preparations such as longer experience, well-known side effects, safety and pharmacokinetics. It is also expected that market availability can influence practice and that the availability of certain products can be determined by different factors such as the cost, company advertisement, central contracts by governmental agencies and clinician's familiarities with certain preparations. Studies in ASPED countries are needed to explore the availability of different preparations used in puberty induction and the impact of access to these medications on clinicians' decision.

The majority of the Arab participants (57.3%) used the age of ≥ 14 years to induce puberty in hypogonadal boys and around 80% of them preferred IM testosterone esters. This choice was comparable to the US survey [11] where 69% induced at ≥ 14 years with 87.8% starting with depot testosterone. The ideal androgen therapy should be safe, affordable and with physiological pharmacokinetics. Therefore, the choice of depot esters by our participants is expected as they fulfill the above criteria and have been in use for more than 50 years. In agreement with most expert opinions [1, 6, 7, 14, 20], the majority (46.5%) of Arab physicians started with 50 mg monthly, while 32.5% used 25 mg and 13.9% used 75 mg. Interestingly, we found a trend of using oral testosterone undecanoate in Gulf states compared to other Arab countries. Given the high resources in these countries, we suspect that this trend reflects patient preference and local availability rather than limited access to the specialist nurse team to administer injections. More than 20% of our responders chose to initiate puberty with nontestosterone preparations (12.3 and 8.64% preferred using HCG and pulsatile gonadotropin, respectively). There was a preference of starting with HCG in non-Gulf Arab countries compared to Gulf states. This regimen was supported by other studies [14, 20, 21] which highlighted its benefits in increasing testicular size and induction of fertility particularly when used in testosterone-naïve boys with childhood hypogonadism.

One limitation to our study is that some responders skipped few questions. However, the average replies for each question were from 83 responders practicing in 17 countries. Although this could reflect a wide opinion in the region, it is worth noticing that there are some variations between these countries in terms of culture, economy and access to medications. Second, some participants were trainees, and it is therefore possible that some of their answers could reflect opinions, based on theoretical knowledge, rather following their consultants' experience. However, in order to minimize the impact of this factor, we

compared the replies of consultants versus trainees and found no significant difference between the two groups apart from one minor result which has been addressed in the discussion. Finally, similar to other survey-based studies, it does not provide accurate assessment of real practice and outcomes.

In summary, we described the practice among ASPED clinicians on the timing and regimen of puberty induction in boys and girls with hypogonadism. The observed variation is expected for clinicians with different training backgrounds practicing in countries with variable resources and health-care system. Further studies on the attitude of patients/parents regarding puberty induction in Arab populations, as well as the availability of estrogen and androgen preparations, and its impact on clinicians' decision are warranted. These studies would provide more insight into the practice in ASPED countries and help in developing regional guideline on the management of puberty induction in children with hypogonadism.

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