Yearbook of Paediatric Endocrinology 2020

Editors
Ken Ong
Ze'ev Hochberg

published by
bioscientifica

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Paediatric Endocrinology 2020

Endorsed by the European Society for Paediatric Endocrinology

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13. Global Health for the Paediatric Endocrinologist

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Preface

Welcome to the 5th edition of this chapter on Global Health in Pediatric Endocrinology and Diabetes. As usual, the selected articles cover most aspects of pediatric endocrinology and diabetes. However, I particularly recommend the first 5 papers that are presented in the first section. They make us reflect on more philosophical aspects of our work as pediatric endocrinologists interested in global health.

Advocacy, History and Society

13.1. Corruption in global health: the open secret *(personal opinion)*

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Lancet 2019; 394: 2119–24.
doi: 10.1016/S0140-6736(19)32527-9

- The author is a physician and has served as Health Minister in her home country, Peru.
- She reviews the role of leaders in low-resource settings in the development of corruption and extends her comments to high-resource environments.
- She discusses 6 types of corruption: absenteeism, informal payments from patients, theft of money, supplies and medications, corruption in service provision, favouritism, and manipulation of data.

This opinion article emphasizes the magnitude and cost of corruption in global health and raises several important issues that we are all facing, sooner or later, knowingly or unknowingly, in our daily practice. How can paediatric endocrinologists ensure that they are not part of the problem and, in addition, that they are part of the solution?

This opinion given by Dr Garcia in her article brings to my mind two examples of difficult situations often faced by paediatric endocrinologists. A first example is the uneasy relationship between the pharmaceutical industry and the paediatric endocrinologist. Over the last 25 years, in order to decrease the conflict of interest between the pharmaceutical industry and the trainees/staff members, ethical rules in North America have prevented perks that used to be common, such as invitations to the annual meeting of professional societies (including flights, meals, registration, and accommodation). While the system is not perfect, in high-income countries, strong institutions and other sources of funding such as universities, non-industry grants or personal resources have made it possible to keep attending many of these precious annual conferences. In low-income countries, where alternative sources of funding are not available and physician's salaries are low, rejecting industry support is much more difficult and leads to difficult choices. How can we ensure that paediatric endocrinologists in low- and high-income countries benefit from the same opportunities? A second example is the lack of access to medicines in many low-income countries (and sometimes also in high-income countries). Why is the medicine that was just prescribed to our patient unavailable, unaffordable or of unsuitable quality? A lack of transparency in the many steps of the process that brings the medicine from the manufacturer to the patient (i.e. cost of production, registration and distribution, tender process, quality control, contracts between various players) plays a major role. Paediatric endocrinologists could and should play a major advocacy role in getting full transparency. While we may think that poor access to medicines is exclusively limited to low-income countries, this is not the case. For instance, a recent BMJ article reports that in August 2019, ASPEN UK admitted taking

part in an anticompetitive arrangement by illegally paying two competitors to secure a monopoly for the distribution of fludrocortisone in UK. This resulted in an 1800% increase in the price paid by the National Health Services (NHS) in UK for fludrocortisone (from 1.5 to 30 GBP for 30 tablets of fludrocortisone). In addition to paying a fine of 8 million GBP, 'Aspen has promised to ensure that in the future there will be at least two suppliers of fludrocortisone in the UK to help the NHS obtain better prices' (reference). As proposed by Dr Garcia in her article, we need to develop 'new models that could work to fight against corruption in global health, and to funders to support this effort'.

Reference

1. Iacobucci G. Drug firms colluded to hike fludrocortisone price by 1800%, says watchdog. *BMJ* 2019;367:l5881.

13.2. The age of paediatrics

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Lancet Child Adolesc Health 2019; 3: 822–30.

doi: 10.1016/S2352-4642(19)30266-4

- The upper age limit of paediatric care varies markedly from country to country.
- The authors surveyed 1372 paediatricians in 115 countries and found that, based on their personal experience, the upper age limit of pediatric services had increased over the last 20 years of their practice, reflecting greater awareness of adolescent health.
- A greater focus on adolescent health during training is recommended.

Between September and December 2018, the authors sent an invitation to participate in an online survey to multiple regional pediatric organisations, asking them to distribute it to their members. The survey focused on the upper age limit of pediatric services in their country and on the respondents' perceptions of the upper age limits of pediatric services 10 years and 20 years ago. The survey was completed by 1372 pediatricians in 115 countries. The highest mean upper age limit of pediatric patients was 19.5 years in the USA. The lowest mean upper age limit was 11.5 years in South Africa. Within a country, replies from pediatricians vary and in 14 countries, the upper age limit varied by more than 10 years. The 600 pediatricians who had practiced for over 20 years reported that the mean upper age limit of inpatients had increased from 16.2 years two decades ago, to 17.4 years now. The main reason for the rising age over time was felt to be a greater awareness of adolescent health and leadership by professional associations. The authors suggest that a greater focus on adolescent health is required within pediatrics to ensure that the future pediatric workforce is appropriately equipped to respond to the changing disease pattern across childhood and adolescence.

Overall, the study shows that there is little agreement on the upper age limit for pediatric care. But should there be an international consensus on the age range of young patients seen by a pediatrician? Interestingly, WHO does not presently have a common definition for the upper age limit of pediatrics. For instance, the Essential Medicine List for children (EMLc) defines a child as younger than 12 years. This means that contraceptives are listed only in the adult EML, not in the EMLc. In the HIV/AIDS section of the WHO website (www.who.int/hiv/pub/guidelines/arv2013/intro/keyterms/en/ adolescence), an adult is a person older than 19 years of age while a child and an adolescent are defined as persons aged <10 and <19 years, respectively. For the WHO growth curves, an adult is a person older than 20 years of age, children as <5 years and school age children $+$ adolescents as 5–19 years. Practically, younger children are commonly seen by a pediatrician, and young adults (after high school) are commonly seen by an adult physician. It can be argued that an international age limit is not realistic and that the age of adolescence should be based on maturation (puberty, independence): age at which adolescents leave home to go to college, work independently or marry; age at which pubertal development and adult height are achieved (for instance, in British Columbia, Canada, the age of transition from

pediatric to adult care is officially flexible, from 17 up to 21 years). There may also be practical reasons that influence the age at which a pediatric patient is cared for by a pediatrician or by an adult physician, such as the availability of pediatric in- and outpatient care (for instance, in francophone Africa, the lack of pediatric endocrinologists means that most children and adolescents are followed by adult endocrinologists). Overall, an important message is that physicians who care for adolescents, whatever the definition is, should receive appropriate specialty and sub-specialty training.

13.3. Effective coverage measurement in maternal, newborn, child, and adolescent health and nutrition: Progress, future prospects, and implications for quality health systems

Marsh AD, Muzigaba M, Diaz T, Requejo J, Jackson D, Chou D, Cresswell JA, Guthold R, Moran AC, Strong KL, Banerjee A, Soucat A, on behalf of the Effective Coverage Think Tank Group
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Lancet Glob Health 2020; 8: e730–36.
doi: 10.1016/S2214-109X(20)30104-2

- Sustainable Development Goals (SDG) were adopted by United Nations Member States in 2015. Universal health coverage is at the centre of SDG #3 but lacks metrics that make it possible to assess how effective the provided healthcare is.
- WHO and UNICEF convened a group of experts, the Effective Coverage Think Tank Group, to develop a consensus on the definition and measurement of effective health coverage for maternal, newborn, child, and adolescent health and nutrition.
- The Group developed a 7-step standardised cascade for the measure of effective coverage that can be applied to various practical situations.

In addition to providing clinical care for patients (and families) with endocrine diseases and with diabetes, pediatric endocrinologists often need to serve as advocates for their patients and their families, especially in settings where universal health coverage does not exist. This is often a difficult task that goes beyond the subspecialty training they receive. The 7-step cascade developed by the Think Tank Group in this article is useful to guide pediatric endocrinologists in their journey as an advocate for their patients. Several practical examples are developed by the authors. Using Type 1 diabetes care as an example, the cascade could be described as follows. Step 1 (target population) consists in identifying the population of children with diabetes (for instance, by improving the diagnosis and by the development of a registry); Step 2 (service contact coverage) consists in determining the proportion of children with diabetes who actually come in contact with the (relevant) health service (for instance, the patient may be known but may not have access to a diabetes team for various reasons such as travel distance, lack of education or poverty); Step 3 (input adjusted coverage) investigates whether the team accessed by the patient is ready to provide the expected care (for instance, there may be insufficient staffing or suboptimal training); Step 4 (intervention coverage) ensures that patients with Type 1 diabetes who come in contact with a diabetes team actually receive the service (for instance follow up may not be available in a timely fashion or language barriers may prevent provision of care); Step 5 (quality-adjusted coverage) determines whether the care is provided according to the expected standards (for instance, the team may not provide care according to internationally-recognized standards such as the ISPAD guidelines or to locally available standards developed for the specific environment of the patient); Step 6 (user adherence-adjusted coverage) assesses whether children with diabetes adhere to provider instructions; Step 7 (outcome-adjusted coverage) investigates whether the provision of optimal care and good adherence to the recommendations actually result in the expected health outcome (for instance, prevention of diabetic complications, decrease in admissions for diabetes keto-acidosis). This framework will be useful to pediatric endocrinologists trying to define a clear process to optimize support for their patients and families with Type 1 diabetes and can be applied to many of our patient groups.

13.4. From dwarves to giants: South American's contribution to the history of growth hormone and related disorders

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Growth Hormone & IGF Research 2020; 50: 48–56.
doi: 10.1016/j.ghir.2019.11.004

- The authors summarize the historical aspects of the discovery of mechanisms underlying short and tall stature in South America.
- Tall stature stories include gigantism in Patagonia, acromegaly and the relationship between glucose metabolism and GH excess.
- Short stature reports include the discovery of GHRH receptor and GH receptor mutations (Laron Syndrome).

This interesting paper mixes history, clinical description and science. It is beautifully illustrated. The first part describes the (tragic) interaction between Spanish sailors, surprised and intimidated by the large size of two populations in Patagonia where they landed during their discovery travels in the 15th and 16th centuries. These populations are now extinct, likely because of diseases brought by the sailors, a stark reminder of the dolorous colonial history in South America, and the cause of the tall stature is unclear. More recently, in the 19th and 20th centuries, the description of tall individuals (most of them with a pituitary adenoma) and the consequences of the disease on the quality of their life serve as a reminder that in all cultures, being different is a cause of discrimination. Many of these giants died early following a life as boxers or circus workers. Finally, at the other hand of the spectrum, the authors describe extremely short people suffering from two medical conditions well-known to pediatric endocrinologists: isolated GH deficiency secondary to an inactivating mutation in the GH-releasing hormone receptor gene, and inactivating mutation of the GH receptor gene (Laron syndrome). The article is also a teaching opportunity and the authors compare the clinical findings of these two conditions found in small communities in Brazil and Ecuador, respectively. Of note, the Ecuadorian patients, who, as research subjects, markedly contributed to our understanding of the growth hormone axis and to the development of recombinant IGF-1, did not benefit from longterm treatment with the expensive medicine that they contributed to develop. It was not provided by the pharmaceutical company and was not paid for by the health system. This situation, which infuriated Dr Guevara-Aguirre (Ecuador) who spent many years following these patients, is a reminder of our duty to protect the patients who participate in the clinical studies they are involved in.

13.5. Branding of subjects affected with genetic syndromes of severe short stature in developing countries

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BMJ Case Rep 2020;13:e231737.
doi: 10.1136/bcr-2019-231737

- The authors report 2 cases of severe short stature, Laron Syndrome and Cornelia-Delange-like syndrome, followed in Ecuador, a country with limited resources.
- They highlight the tendency of a society to discuss children with severe short stature with derogatory terms to automatically assume that these children have developmental delay.
- They also describe the shortcomings in diagnosis and management faced by these patients in low-resource settings.

This article is an opportunity to reflect on our role as clinicians, researchers but also advocates. It mixes history, science and clinical care. It focuses on two issues: the first one is the derogatory terms by which short patients are called ('dwarfs', 'midgets') and the second is the lack of resources in many low income countries that lead to suboptimal assessment and management. The first issue is unfortunately not limited to low income countries. Being different is often a reason for discrimination, and extreme short stature is a clear example. In our work as pediatric endocrinologists, short stature is a very common reason for referral, reflecting the perceived importance of height in the society. The authors highlight the consequences, not of the short stature per se, but of the discrimination associated with the short stature on the quality of life of patients. This should lead us to reflect on our role as advocates for our patients. The second issue is more specific to low-resource settings, where expensive diagnostic tests and treatments are often difficult to obtain. Again, as pediatric endocrinologists, we need to learn how to collaborate, communicate and advocate for access to diagnostic tests and to medicines. Our task also consists in ensuring that we make the best use of limited resources.

Diabetes

13.6. Management of diabetes during Ramadan fasting in children and adolescents: A survey of physicians' perceptions and practices in the Arab Society for Paediatric Endocrinology and Diabetes (ASPED) countries

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Diabetes Res Clin Pract 2019; 150: 274–281.
doi: 10.1016/j.diabres.2018.12.014

- An online survey was sent to physicians registered with the Arab Society for Paediatric Endocrinology and Diabetes (ASPED) to assess the attitudes of health professionals in the management of Type 1 diabetes during Ramadan.
- There were 167 responders (86% were pediatricians, 14% were adult physicians).
- Almost 80% of the physicians would allow their patients to fast. Attitudes varied markedly among the health professionals surveyed (mainly pediatricians) regarding the prevention and management of both hypo- and hyperglycemia.

The results of the survey show that close to 80% of the surveyed physicians would allow patients to fast. Only a small majority (61%) emphasized the importance of providing education before fasting. Those with hypoglycemia unawareness were considered as high-risk patients for fasting by 47% of physicians. A majority (62%) felt that fasting should be broken if symptomatic hypoglycemia develops. In terms of management, a majority of respondents would decrease basal insulin by 25%, would recommend several dietary adjustments and would use rapid-acting insulin analogs and carbohydrate counting. This article is relevant to pediatric endocrinologists all over the world who care for Muslim children and adolescents with Type 1 diabetes. It complements another article (reference) that provides guidelines for the management of Type 1 (and Type 2) diabetes during Ramadan fasting. The survey shows that the attitudes towards Ramadan fasting vary widely between health professionals not only regarding the criteria required for permission to fast safely but also regarding the management guidelines. I had the opportunity of discussing this interesting issue with a Muslim colleague who also has Type 1 diabetes in order to better understand her point of view. First, she mentioned that, although Ramadan fasting is a pillar of Islam, it is very clearly written that fast can be broken if it may lead to self-harm, such as with diabetes. It is a sin to harm yourself in these circumstances. However, not fasting, or eating food in public, even for permitted reasons, can result in bullying of the children and can lead to discrimination, emphasizing the importance of social norms and of education. Second, it is clearly taught that injecting insulin is not regarded as breaking the fast. In contrast, injecting glucagon or IV glucose is considered

as breaking the fast, although it is, as mentioned above, permitted in patients with Type 1 diabetes. Finally, the survey appropriately mentions that monitoring of Type 1 diabetes must be more stringent during fasting. However, for patients in resource-limited settings who have access only to human insulin, or for those who cannot afford to pay for more than 1–2 strips a day, optimizing diabetes management is more challenging than for those who have access to insulin pump, long-acting analogues, appropriate number of glucose strips or glucagon. Thus, proposing the most appropriate options for Ramadan fasting needs to take into account the individual circumstances of each patient and family.

Reference

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13.7. Smartphone-based, rapid, wide-field fundus photography for diagnosis of pediatric retinal diseases

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Trans Vis Sci Tech. 2019; 8(3):29.
doi: 10.1167/tvst.8.3.29

- This study investigates the feasibility of acquiring diagnostic quality fundus photographs in children using a child-friendly smartphone.
- Photographs were acquired in 43 patients (mean age 6.7 years) with i.e. retinoblastoma, Coats' disease, commotio retinae and optic nerve hypoplasia.
- There was 96% agreement between image-based diagnosis and the treating clinician's diagnosis. This device, which can acquire fundus photos in 2.3 minutes and is well-tolerated, brings the possibility of easily assessing retinal disease in children with diabetes.

This article shows us what the future could look like for children and adolescents with diabetes living in low resource-settings. The concept of 'point of care testing' (POC), where investigations are performed directly where the patient lives (instead of having the patient travel to a center where equipment is present) is developing fast. The authors developed a portable handheld smartphone-based retinal camera (like the one used in an i-phone). The device captures high-quality fundus images, stores them, and transmits them via the wireless communication system of the device for remote evaluation. This is a welcome innovation in countries where children with Type 1 diabetes experience early and severe diabetic complications and insufficient screening for these complications. It has many potential applications in pediatric endocrinology and diabetes. One of the most attractive is the use of POC testing for the neonatal screening for congenital hypothyroidism. In many low-resource settings, mothers deliver at home, time-sensitive shipment of samples is not feasible, central laboratories are non-existent, and recall of patients is difficult. POC testing could be performed by a visiting allied health professional who could then contact a specialist in case of positive results. It is hoped that in the coming few years, a variety of POC tests will be available for large scale use, bringing to children in developing countries the care they deserve.

13.8. Diabetic microvascular complications among children and adolescents in northwestern Tanzania: A cross-sectional study

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Annals of Global Health. 2020; 86(1): 43, 1–8.
doi: https://doi.org/10.5334/aogh.2669

- The authors assessed the prevalence of diabetic microvascular complications in 155 children and adolescents with Type 1 diabetes in northwestern Tanzania.
- They observed poor diabetes control in 69% of the patients and a high rate of diabetic nephropathy (32.9%), retinopathy (10.3%) and neuropathy (13.6%).
- Innovative initiatives are needed to optimize glycemic control.

Over the last 10–20 years there has been a marked increase in capacity in pediatric endocrinology in sub-Saharan Africa. This has led to the understanding that, like other parts of the world, Type 1 diabetes is not uncommon in African children and adolescents. Unfortunately, microvascular complications appear early in a high percentage of patients. Not surprisingly, in their study, prevalence of microvascular complications was significantly associated with older age (adolescence), poor glycemic control (HbA1c >12.5%) and longer duration of diabetes (>5 years), although the latter association was only statistically significant in univariate analysis. While a genetic predisposition of African patients cannot be ruled out, it is likely that the high rate of early microvascular complications is due to a combination of environmental factors such as insufficient number of trained allied health professionals, lack of access to insulin (although organisations such as Changing Diabetes in Children and Life for a Child support access to insulin and supplies for children with Type 1 diabetes in Tanzania and elsewhere) or high price of glucose strips resulting in poor blood glucose monitoring. These aspects of diabetes care are unfortunately not discussed by the authors. The authors also make the interesting point that pre-existing renal disease (such as renal disease secondary to schistosomiasis) may contribute to the high rate of nephropathy, highlighting the need for guidelines that meet the specific needs of a population. To my knowledge, such guidelines are not commonly available for children and adolescents with diabetes living in low resource settings.

Endocrinology

13.9. People are taller in countries with better environmental conditions

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Front. Endocrinol. 2020; 11:106.
doi: 10.3389/fendo.2020.00106

- The authors assessed the relationship between markers of a stressful environment and final height in adult men and women in 71 countries (including 31 countries that are members of the Organisation for Economic Co-operation and Development [OECD]).
- They found that the more stressful the environment, the shorter the adult height.
- By order of decreasing importance, the relationship between markers of a stressful environment and height were income inequality > air pollution > growth domestic product > corruption perception index > homicide rate > life expectancy > unemployment.

Overall, this interesting article suggests that the better the environment (defined by 7 equally weighted indicators of a stressful environment: homicide rates, growth domestic product per capita, income inequality, corruption perception index, unemployment rate, urban air pollution and life expectancy), the greater the final adult height. The authors consider the relationship between environment and height at the global level and rank final height according to published characteristics of each country. Several comments come to mind. First, they mention that the within-country variability is similar to the between-country variability. However, published data do not make it possible to determine whether the within-country variability is affected by the same stressors as the between-country variability. For instance, within a country, are children less affected by an adverse environment growing faster then those more affected by these stressors? Second, it is important to understand the relationship between qualitative and quantitative nutrition, a key determinant of linear growth, and the various environmental markers

used in this study. For instance, is income inequality affecting growth because poorer people have less money to buy food or because they live in less desirable areas where air pollution is higher, chronic diseases more common and psychological stress due to lack of safety greater? The most likely assumption is that it may be a combination of several factors. Third, the study focuses on final height as a marker for growth in childhood and adolescence, but it is also conceivable that this growth is affected by prenatal factors (maternal environment) and opens the door to the concept of transgenerational effect of stress. Finally, at the individual level, short stature is one of the most common reasons why patients are referred to a pediatric endocrinologist. Although pediatric endocrinologists are asked to rule our hormonal deficiency or excess as a cause of short stature, they are well aware that height variation results from a complex interaction between genetic, environmental, socioeconomic, and cultural factors. An example relevant to this article is psychosocial short stature, which is caused by stress and emotional deprivation in children (usually within the family), is associated with low height velocity (that increases back to normal once the stressors are removed) and, provided that the stressors are removed early enough in life, with normal or near normal final height. It is thought to be mediated at least in part by functional, reversible growth hormone deficiency secondary to hypopituitarism and is mostly independent from nutrition. At the clinical practice level, this article is a reminder to have a broad approach when assessing a patient for short stature.

13.10. Timing of the infancy-childhood growth transition in rural Gambia

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Front. Endocrinol. 2020 11:142.
doi: 10.3389/fendo.2020.00142

- A delayed transition from the infancy to the childhood growth stage contributes to sub-optimal growth outcomes.
- Using a novel method to assess the timing of infancy-childhood transition (quantification of patterns of adjacent monthly weight-for-age z-score (WAZ) deviation correlations), this transition was found to take place at the age of 12 months in UK. The authors in this study find that the transition takes place earlier in rural Gambia (9 months).
- The authors hypothesize that while a later transition allows maximal extension of the high rates of growth during the infancy, an earlier transition may negatively affect the growth outcomes in childhood but also offers an extended window for later catch-up.

This article is to some extent complementary to the article by German et al. discussed above. The model of Karlberg on which this article is based defines the infant-childhood transition as the period during which the rapid infantile growth decreases towards the more stable state and growth rate plateau of childhood. It is postulated to be associated to a progressive shift from the leading role of insulin and the insulin-like growth factors as mediators of nutritional status in the fetus to the role of the endogenous regulation of growth hormone. At that time, the child enters his/her defined percentile of growth. To assess the timing of this shift, the authors examine the change in the month-to-month correlation of the weight for age *Z* scores (WAZ). The shift in the correlations between adjacent WAZ from positive to negative values is associated with a change from infantile to childhood growth. Because of the importance of early growth for the development of long-term complications in the child, understanding the variation and factors in the timing of transition could be very useful if some of the factors could be modified to positively affect growth. In two UK studies, this shift was found to take place around the age of 12 months. Surprisingly, in the present study, applying the same modeling as the UK studies, the transition in rural Gambia was found to take place earlier, at 9 months. Assuming that the technical limitations of this complicated model do not affect the interpretation of the results, why would the transition from infancy to childhood take place earlier in Gambia compared to UK? It may reflect a trade-off: when energetic resources are limited and are prioritized for immediate, life-saving tasks

(such as fighting infections), rapid growth takes a back seat to ensure that the remaining resources can still support key tasks such as brain development. Catch-up growth may take place later is energetic resources are again plentiful. From a philosophical point of view, it may be that ponderal (and therefore linear) growth should not take place at the detriment of higher functions.

13.11. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis

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JAMA Pediatr. 2020;174(4):e195881.
doi: 10.1001/jamapediatrics.2019.5881

- The authors evaluated the change in pubertal onset in healthy girls around the world based on age at thelarche.
- Overall, the age at thelarche decreased 0.24 years per decade from 1977 to 2013.
- This decrease seems to reflect a worldwide trend.

The authors focus on the change in the age of apparition of breast development in girls living in different parts of the world. Despite many limitations that are expected in a meta-analysis of published studies, they show a worldwide decrease in the age of thelarche of about 3 months per decade. This is consistent with the decrease in the age of menarche of 2–6 months per decade reported in many countries around the world over the last 40 years, including India, China, Ghana, and Korea. A major cause for this earlier activation of the hypothalamo-pituitary-gonadal axis is thought to be improved nutrition in children and, in particular in the United States, a major increase in the prevalence of obesity. The common link seems to be an increased production of leptin by the adipose tissue which in turns activates the hormonal cascade leading to the development of puberty. However, the role of endocrine disruptors, rarely measured in low-resource settings, is also postulated. The present article also finds that the mean age at thelarche ranged from 9.8 to 10.8 years in Europe, 9.7 to 10.3 years in the Middle East, 8.9 to 11.5 years in Asia, 8.8 to 10.3 years in the United States, and 10.1 to 13.2 years in Africa. From a clinical point of view, these data have implications on the use of diagnostic and therapeutic agents, in particular in low-resource settings where healthcare funding is limited. Traditional recommendations include determination of basal or stimulated LH and FSH, MRI of the hypothalamo-pituitary region, bone age and pelvic ultrasound to rule out an underlying condition in girls presenting with precocious puberty. However, pediatric endocrinologists know that in the vast majority of the cases, the final diagnosis will be idiopathic central precocious puberty. This suggests that the age at which evaluation of the child with precocious puberty should be considered should be adapted to the local characteristics and that evaluation should rely on clinical examination and follow up, with investigations performed only in children who are at high risk of an underlying condition.

13.12. Global trends in insufficient physical activity among adolescents: A pooled analysis of 298 population-based surveys with 1.6 million participants

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Lancet Child Adolesc Health 2020; 4: 23–35.
doi: 10.1016/S2352-4642(19)30323-2

- The study reports the worldwide prevalence of insufficient physical activity among school-going adolescents aged 11–17 years.
- Data from surveys totalling 1.6 million students aged 11–17 years were analysed.
- The majority of adolescents do not presently meet physical activity guidelines.

WHO set a global target of a 15% relative reduction of insufficient physical activity among adolescents and adults by 2030. Insufficient physical activity was defined as not reaching the current WHO recommendation of 60 min of daily physical activity of moderate-to-vigorous intensity. Indeed, the health benefits of a physically active lifestyle during adolescence are important for the prevention of non communicable diseases through positive effects on weight, on cardiorespiratory and muscular fitness and on cardiometabolic health. Overall, the results of this study show that insufficient physical activity has remained similar or (in boys only) has slightly decreased in adolescents aged 11–17 years between 2001 and 2016. These results, which are not encouraging, need to be interpreted cautiously. First, the authors evaluated physical activity indirectly, through questionnaires, and it is highly possible that simple questions about physical activity may not reflect true physical activity. Second, compared to high-income countries, there was a dearth of data in low-income countries. In fact, data were not available for many countries in sub-Saharan Africa. Finally, culture may affect how questions are understood and answered in different countries. Nevertheless, it seems that few changes in physical activity have taken place over a 15-year period and that the results are similar in all parts of the world. Unfortunately, the study does not provide information on the determinants of physical activity and on how these determinants may differ in different countries. These are arguably key questions for those tasked with developing public health measures. Adolescent activity (or lack thereof) remains a true global issue that needs to be addressed if one hopes to prevent the rapid progression of non-communicable diseases and their cost to fragile health systems.

13.13. Prevalence of vitamin D deficiency in Africa: A systematic review and meta-analysis

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Lancet Glob Health 2020;8: e134–42.
doi: 10.1016/S2214-109X(19)30457-7

- The results of 25OH Vit D determination from 129 studies including 21 474 participants in 23 African countries were analyzed.
- Overall, a serum 25(OH)D concentration less than 30 nmol/L was found in 18.5% of the population and less than 75 nmol/l in 59.5% of the population.
- Newborn babies, women and those living in urban areas were found to be at higher risk for low 25OH Vit D.

The article describes the magnitude of 25(OH)vitamin D (25(OH)D) deficiency in many African countries and highlights its role in the high prevalence of rickets reported in Africa. The authors do not comment on the potential reasons for the marked disparities in vitamin D deficiency between countries. For instance, the difference in mean 25(OH)D concentration in Ethiopia (46.5 nmol/l) compared to neighbouring Uganda (82.5 nmol/l) is striking. Is it due to different cultures/lifestyles (the Muslim population represents 12% in Uganda and 34% in Ethiopia), study bias (most of the studies are regional), government policies promoting administration of vitamin D, or to other factors? Many of the risk factors are difficult to modify, i.e. urban living (an increasing proportion of the population lives in cities), female sex (women tend to stay home more than men and, when going out, are more covered than men); geographical location away from the equator (where the sun's UVs are less effective in generating vitamin D) and darker skin (which is less adapted to vitamin D synthesis). It is important to note that while the prevalence of rickets is generally high in Africa, 25(OH)D deficiency may not be the sole culprit. The consumption of milk (a major source of calcium) tends to be low in parts of Africa (for

instance, 62 liters per capita per year in Uganda, which is similar to Europe and North America compared to 20 liters in Ethiopia). Overall, there seems to be enough data to support the development of government policies that promote vitamin D (and calcium) supplementation. The actual process for supplementation needs to be carefully considered: general supplementation vs focus on at-risk population (pregnant mothers and young children), oral vs parenteral administration of vitamin D (the presence of malabsorption may prevent absorption of oral vitamin D), over the counter vitamin supplements vs. food fortification (such as milk).

13.14. Newborn screening in Nigeria: Will incorporating congenital hypothyroidism with sickle cell disease improve neonatal screening programme?

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Acta Biomed. 2019; 90(2): 316–320.
doi: 10.23750/abm.v90i2.8485

- The authors review the present status of newborn screening in Africa and discuss the concept that adding a neonatal screening for congenital hypothyroidism (CH) to an existing sickle cell disease screening would make it easier to implement than developing an independent screening program.
- Structure, funding, political will and an efficient recall system are identified as being key requirements for the development of a successful neonatal screening for CH.

This article considers important aspects around the practical approach towards the development of a successful newborn screening (NBS) program for congenital hypothyroidism (CH) in Nigeria, a resource-limited country. As we all know, NBS for CH is routinely performed in high-resource countries since the 1970's. First, the authors discuss whether there could be a synergy between the NBS for sickle cell disease (SCD) and for CH. This was contemplated in neighbouring Ghana where NBS for SCD has been piloted for many years at Komfo Anokye Teaching Hospital (KATH) in Kumasi. The SCD program is available on the first day of life to the babies born in this tertiary care center, where the samples are analyzed. The program remains active at KATH, but a lack of funding may jeopardize sustainable continuation of the program and its extension to the rest of the country. The addition of an NBS program for CH that would build on the existing infrastructure of the NBS program for SCD has been discussed but is presently not supported by the health authorities (Dr E Ameyaw, personal communication). Second, the development of an NBS for CH needs to consider the specificities of the country and can not be based simply on the protocols used in well-resourced countries. This was addressed in the recent guidelines for development of NBS for CH in India, including the option to measure TSH on a cord blood sample and the use of local laboratories to perform TSH determination. Indeed, several issues are specific to low-resource countries, including lack of a central laboratory, difficulty to trace positive patients, large number of at home deliveries and non-existence of a reliable system to ship samples. Finally, although not mentioned by the authors, point of care (POC) testing for TSH needs to be considered. It is available for NBS for SCD and such a test is being considered for inclusion in the 2020 WHO Model List of Essential In Vitro Diagnostics. Unfortunately, a reliable test is not yet available for TSH, although large-scale testing is being considered by several companies. Such a POC test for TSH would make it possible to have an immediate diagnosis for patients irrespective from where they live or where they were born.

13.15. Adverse outcomes and economic burden of congenital adrenal hyperplasia late diagnosis in the newborn screening absence

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J Endocrine Society 2020; 4 (2): 1–13.
doi: 10.1210/jendso/bvz013

- The authors performed a retrospective analysis of the economic burden in a cohort of 195 patients with genetically confirmed CAH born in São Paulo where there is presently no neonatal screening for CAH.
- The cost associated to mortality of undiagnosed patients was estimated to range from $2 239 744 to $10 271 591 per year.
- The mean total cost until 19 years of age (diagnosis, standard treatment, and adverse outcomes) was much higher for a patient with salt wasting CAH ($89 349) compared to a patient with simple virilizing CAH ($5922).

This study is the first step towards a cost-effectiveness analysis that will compare the cost of caring for patients with congenital adrenal hyperplasia (CAH) with and without the implementation of a newborn screening program for CAH. Presently, this screening does not exist in São Paulo. The authors estimate the medical cost of caring for patients with CAH from birth to 19 years. They should be commended for their attempt to include in this analysis as many aspects as possible of treatment cost, including mortality (unrecognized affected patients), dehydration, mental impairment, hospitalization, hormonal determinations, medicines for standard (corticosteroids) and extended (GnRh analogues and growth hormone because of late diagnosis) medical treatment. Their experience brings to mind several comments. First, like many countries where neonatal screening is not available, there is an excess of female compared to male patients, reflecting the greater difficulty to diagnose CAH in male neonates in the absence of genital abnormalities. However, the percent of male neonates diagnosed clinically with CAH has increased markedly from before 1989 (25%) to after 1999 (41.7%) thanks to increased early recognition. Second, sex assignment error (male sex wrongly assigned to female neonates) emphasizes the importance of performing a thorough medical examination of each neonate, an issue common to many low resource settings. Third, the authors could not estimate the effect of sex error assignment or late diagnosis (with more severe virilization) on quality of life and on psychological outcomes. Whether or not, in the Brazilian context, the future financial analysis will show that a neonatal screening would be cost-effective remains to be seen. However, from a human perspective, prevention of neonatal deaths, prevention of mental retardation, less severe virilization and proper sex assignment may be regarded as priceless.

13.16. Assessment of health-related quality of life in Egyptian children and adolescents with congenital adrenal hyperplasia

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J Pediatr Endocrinol Metab 2020; 33(2): 295–304.
doi: 10.1515/jpem-2019-0345

- Using the validated World Health Organization QOL-BREF questionnaire that independently assesses the physical, psychological, social and environmental domains, the authors assessed health-related QOL in 200 Egyptian children and adolescents with CAH.
- Older patients had significantly lower QOL scores ($r=-0.151$, $P=0.033$). The physical domain correlated significantly with the degree of virilisation ($r=-0.491$, $P=0.001$) and frequency of hospitalization ($r=-0.495$, $P<0.001$). The psychological domain was affected by age ($r=-0.157$, $P=0.026$) and timing of genitoplasty ($r=-0.326$, $P=0.001$), while the social domain was affected by age ($r=-0.277$, $P<0.005$) and pubertal stage ($r=-0.195$, $P=0.006$). Salt wasting patients had lower scores at the physical domain ($P=0.001$).
- Health-related QOL worsened with older age, poor hormonal control and high frequency of hospital admissions.

This cross-sectional study included 140 females and 60 males with CAH due to 21-hydroxylase deficiency (mean age 6.6 ± 4.5 years). The WHO questionnaire (WHOQOL-BREF) used by the authors assesses four main domains: physical health (i.e. activities of daily living, dependence on medicines, energy, mobility, pain), psychological health (i.e. body image, negative and positive feelings, self-esteem, learning), social relationships (i.e. social support) and environment (i.e. financial resources, freedom, physical safety, home and physical environments, leisure activities). Overall, children and adolescents with CAH were found to have a lower QOL compared to a general population. Although there was no control group in this study, the version of the

WHOQOL-BREF in Arabic was found to have excellent reliability and validity. Females had lower scores at the psychological domain, whereas males had lower scores at the physical domain. Several aspects of this interesting article deserve comments. First, 77/137 neonates originally assigned to the male sex were later reassigned to the female sex after confirmation of the diagnosis. Although the age at which reassignment was performed is not provided, final diagnosis was obtained at a median age of 4 days, but as late as 10 years. While the questionnaire was administered only to the children (with the help of the parents when needed), it would be interesting to understand the impact of sex reassignment on the parents themselves. Second, in this Egyptian study, clitoroplasty was performed at a young age. The younger the age, the better the psychological component of the QOL. An Arab colleague helped me put this article in the context of her culture. She explained to me the influence of social norms on the timing of the decision of the surgery. Some will argue that surgery should be delayed until the child can make the decision herself. In Egypt (where 85–90% of the population is Muslim), it is important that cosmetic normalization be performed as early as possible regardless of a medical indication. Indeed, in most Arab societies, genital ambiguity affects the family social well-being, sexuality is not openly discussed (and a question about sexual pleasure was removed from the questionnaire), homosexuality is not recognized, assisted reproduction options are limited (*in vitro* fertilization and intrauterine insemination between the spouses are permitted but egg and sperm donation from unrelated donors are not) and women who are unmarried or do not conceive face many social issues. Many of the female patients included in this study were very young, and it would be important to reassess the QOL when they become adults to understand the long term effects of CAH, which can adversely affect fertility and sexual function. This article serves as a reminder that guidelines for the management of CAH need to consider the culture and religion of each population.