

## «A Window of opportunity»

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As clinicians we are trained to observe clinical cues and develop differential diagnoses. Often we are inclined to consider the most likely possibilities, yet for patients with rare disorders, this can result in lengthy delays in diagnosis. Indeed, patients with rare diseases are often initially misdiagnosed and have delays in obtaining an accurate diagnosis<sup>1)</sup>. Misdiagnosis and delays in reaching a correct diagnosis can have significant repercussions on quality of life and can erode confidence in the health system. Recently, there has been growing attention to early life determinants of health and disease. This article provides a brief overview of how phenotypes in male neonates can provide important clues that provide a neonatal window of opportunity for making an early diagnosis of disorders of puberty and reproduction later in life<sup>2)</sup>.

**The importance of the neonatal mini-puberty**  
From the first week through approximately 6-months of life, the hypothalamic-pituitary-gonadal (HPG) axis is activated and this results in serum hormone levels in similar to adults<sup>3)</sup>. Indeed, this is sometimes evident as «baby acne» and male infants may have erections observed during diaper changes. In male infants the increased levels of gonadotropins, luteinising hormone (LH) and follicle stimulating hormone (FSH) stimulate testicular development (i.e. Sertoli cell and spermatogonia proliferation) as well as testosterone production<sup>4)</sup>. This so called «mini-puberty» has proliferative effects that are thought to significantly impact future fertility. Conversely, males who lack this developmental hormonal surge, such as patients with congenital hypogonadotropic hypogonadism (CHH), Kallmann syndrome (KS) or combined pituitary hormone deficiency (CPHD), can have impaired puberty and fertility later in life<sup>5)</sup>. Importantly, there are clinical clues at birth that can help identify patients who have absent mini-puberty.

Red flags of absent minipuberty: undescended testes and micropenis. Androgens (i.e.

testosterone, dihydrotestosterone) are critical for testicular descent and penile growth during early life development. During fetal life, maternal chorionic gonadotropin stimulates the testes and is critical for masculinizing the male genitalia. Yet LH is needed for further penile growth and testicular descent, thus for males with disrupted HPG axis (i.e. CHH, KS, CPHD with LH/FSH deficiency) who lack LH secretion, this may be clinically manifested as undescended testes with or without micropenis<sup>5),6)</sup>. Males with cryptorchidism have reduced numbers of Sertoli cells and spermatogonia and have increased risk for infertility later in life<sup>4)</sup>. Swiss researchers using histological analyses have demonstrated the negative impact that undescended testes can have on spermatogenic potential<sup>7)</sup>. This can be mitigated by surgical correction (orchiopexy within the first year of life) and micropenis can be effectively treated with androgens during early infancy<sup>6)</sup>. Moreover, several small studies employing hormonal treatment during the neonatal window hold promise for optimizing future fertility - yet longterm follow up of these children is needed to determine the impact on fertility<sup>8)</sup>. While these early interventions can have beneficial effects on future fertility potential, often the window of opportunity to diagnose CHH, KS, CPHD is missed.

**Confirming clinical suspicion**  
Identifying CHH, KS and CPHD (with LH/FSH deficiency) can be accomplished in one of two ways: by identifying mutations in known disease loci using genetic testing or via hormonal profiling (testosterone, LH, FSH) during the mini-puberty - when the HPG axis is active in the first months of life. Genetic testing can be informative yet only a small proportion of cases are accounted for by the known CPHD loci and 25+ genes that have been shown to underlie CHH/KS<sup>6)</sup>. Moreover, the loci for CHH/KS only account for approximately half of cases. This should not be a deterrent for genetic screening. Rather, it can complement hormone screening (between 1 week and 6-months of life)<sup>6)</sup>. Notably a program led by

Dr. Franziska Phan-Hug has been initiated at the CHUV to systematically screen male infants born with cryptorchidism/micropenis. Unfortunately, all too often this window of opportunity is missed.

**Impact of missed diagnostic opportunities**  
Even in situations when patients have a medical history of corrected undescended testes or treated micropenis, these clues are often not taken into account when patients subsequently present for failing to spontaneously initiate puberty. Delayed diagnosis for adolescents and young men with CHH/KS is not infrequent. A recent report identified that men were diagnosed quite late (95% CI: 17.6-20.2 years) and this delay has significant impact on psychosocial wellbeing including feelings of isolation, shame, body image concerns as well as negative effects on psychosexual development<sup>10)</sup>. Thus attention to these red flags can enable a timely diagnosis and appropriate timing of treatment. This is important as initiating treatment to induce secondary sexual characteristics in line with peers can help ameliorate some of the psychological impact experienced by these men - who if left untreated, are essentially young adults trapped in an unvirilized child's body. This is reflected in a quote of a patient with CHH «All those things are seeds for psychological damage. I mean, the stuff occurring at that stage (adolescence) builds up and builds up and builds up over the years...».

In summary, the mini-puberty of neonatal life is a remarkable biologic event that appears to have significant impact on future reproductive health. Signs including cryptorchidism and micropenis are important red flags raising the suspicion of congenital disorders affecting puberty and reproduction. It is worthwhile to note that cryptorchidism occurs in 2-5% of males<sup>6)</sup> and certainly not all of these cases will have an underlying rare disorder. However, clinicians should be aware that appropriate evaluation of such cases can identify patients early and timely diagnosis can have major benefits for optimizing potential fertility and may be a life-changing help to prevent or decrease psychological morbidity and enhance quality of life for these patients.

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