

Mini-Review

Congenital Micropenis: Etiology And Management

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Abbreviations: AMH, anti-Müllerian hormone; AR, androgen receptor; CHH, congenital hypogonadotropic hypogonadism; DHT, dihydrotestosterone; Dkk2, Dickkopf-related protein 2; DSD, differences/disorders of sexual development; FSH, follicle-stimulating hormone; GT, genital tubercle; hCG, human chorionic gonadotropin; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone (GnRH); PAIS, partial androgen insensitivity syndrome; SDS, standard deviation score; SPL, stretched penile length; Wnt, Wingless-related integration site.

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Abstract

In the newborn, penile length is determined by a number of androgen dependent and independent factors. The current literature suggests that there are interracial differences in stretched penile length in the newborn and although congenital micropenis should be defined as a stretched penile length of less than 2.5 SDS of the mean for the corresponding population and gestation, a pragmatic approach would be to evaluate all boys with a stretched penile length below 2 cm, as congenital micropenis can be a marker for a wide range of endocrine conditions. However, it remains unclear as to whether the state of micropenis, itself, is associated with any long-term consequences. There is a lack of systematic studies comparing the impact of different therapeutic options on long-term outcomes, in terms of genital appearance, quality of life, and sexual satisfaction. To date, research has been hampered by a small sample size and inclusion of a wide range of heterogeneous diagnoses; for these reasons, condition-specific outcomes have been difficult to compare between studies. Lastly, there is a need for a greater collaborative effort in collecting standardized data so that all real-world or experimental interventions performed at an early age can be studied systematically into adulthood.

Key Words: micropenis, testosterone, gonadotropins, DSD

The term congenital micropenis is used in clinical practice to refer to a penis that is shorter than expected for a newborn male infant [1]. Given that length is a continuum, the

definition of a micropenis is relatively arbitrary. However, the identification of a micropenis is important as it may indicate an underlying health condition that requires further

investigation. Congenital micropenis may be associated with psychosocial distress in parents [2] and although it is reported that young adults with this condition may suffer from a poorer quality of life [3-5], this finding is not universal [6]. Often, the initial evaluation and management of congenital micropenis has involved the administration of androgens to the young infant with a view to enlarging the penile size. However, the effectiveness of this therapy, especially as far as long-term outcome goes, remains questionable. It is expected that a clearer understanding of penile development, normal variations, the pathophysiology of micropenis, as well as standardized long-term follow-up will improve this condition's management. This review will cover these aspects and identify areas for future research.

Development of the Penis

Penile development is a complex multistep process. While the role of androgens in the masculinization of the external genitalia is indisputable, there are specific aspects of penile development that are also dependent on factors other than androgens [6]. The human penis develops from the genital tubercle (GT), an elevation of the perineum, already recognizable at 5 to 6 weeks of gestation as a pair of buds, the genital swellings, on the either side of the cloacal membrane [7, 8]. Signaling through Fgf (fibroblast growth factor), Wnt (Wingless-related integration site) and Shh (Sonic hedgehog) has been recently identified in the initiation and maintenance of genital budding and their concerted action may be critical for preparing mesenchymal competency for androgen action [7, 9]. Wnt/ β -catenin signaling has been implicated in the regulation of multiple developmental processes, such as cell proliferation, differentiation, and cell migration. Activation of the β -catenin signaling pathway is necessary for GT masculinization [9]. The critical role of this pathway is further supported by the finding that genetically modified female mice with constitutively activated β -catenin signaling show male-type external genitalia. In addition, Dkk2 (Dickkopf-related protein 2), which encodes an extracellular antagonist of canonical Wnt/ β -catenin signaling, is highly expressed in female GT mesenchyme (Fig. 1). In the male GT, Dkk2 is regulated negatively by the androgen receptor (AR) which plays a transcriptional repressor role by modulating histone methylation via recruitment of LSD1 (lysine-specific histone demethylase 1) [10] (Fig. 1). There is further experimental evidence in the mouse, indicating that androgen-induced genes that are responsible for masculinization of the external genitalia may be epigenetically regulated by SP1 (Specificity protein 1), a ubiquitously expressed transcription factor that regulates a range of housekeeping and tissue-specific genes [11] (Fig. 1). It is also possible

that there are some master regulating genes, such as AP-1 (Activator protein 1), that also play a critical role in modulating genital development and identification of these will provide further insight into future therapeutic strategies for micropenis [12].

In humans, the GT contains tissue derived from all 3 germ layers: the ectoderm, from which the skin of phallus and prepuce will develop; the mesoderm, from which the corporal bodies will develop; and, the endoderm, forming the urethral plate, which will give rise to the penile urethra [13]. In humans, before the tenth week of gestation, the GT in males and females appears identical in size and morphology [14, 15]. At about 9 to 10 weeks of gestation, when gonadal differentiation of the bipotential gonad has begun, the urethral plate begins to canalize, forming a wide diamond-shaped groove on the ventral surface of the male genital tubercle. The lateral urethral folds of the groove then fuse in the ventral midline, creating the tubular urethra within the penile shaft [15, 16]. At this stage, testosterone and dihydrotestosterone (DHT) play a key role through their action on the AR, expressed in the epithelium and mesenchyme of the urethral folds [17, 18]. From 8 to 18 weeks of gestation, penile length significantly increases from 0.5 mm to 8 mm in humans [19]. This period corresponds to the increased production of testosterone by fetal testis, documented as 150 to 400 ng/dL (5.2-13.9 nmol/L) [6, 17]. After that, fetal testosterone production decreases, remaining stable at less than 100 ng/dL (3.5 nmol/L) until birth [6, 17]. However, between 20 weeks of gestation and birth, the penis may grow an additional 2 cm, before reaching its full newborn length [15, 16]. Thus, penile growth in humans is strictly regulated by androgens during the early weeks of gestation, at the time of minipuberty, and during puberty; however, other hormonal pathways may contribute to penile growth from 20 weeks of gestation until the point of minipuberty and from 6 to 8 months of age until puberty [15, 19]. Several reports have suggested that growth hormone and IGF1 may be involved in penile growth [6, 20]. Moreover, in healthy term newborns, penile length has been shown to correlate to other markers of prenatal androgenization such as anogenital distance [21], and penile length may also show an association to birth length [22], highlighting the overlapping role played by determinants of skeletal and genital development.

Environment and Epidemiology

The detrimental effect of environmental prenatal exposure to endocrine disruptors on the androgenization of male offspring has been described for more than 3 decades now [23, 24]. This has also been supported by other observations, such as the reports of micropenis in cases of prenatal

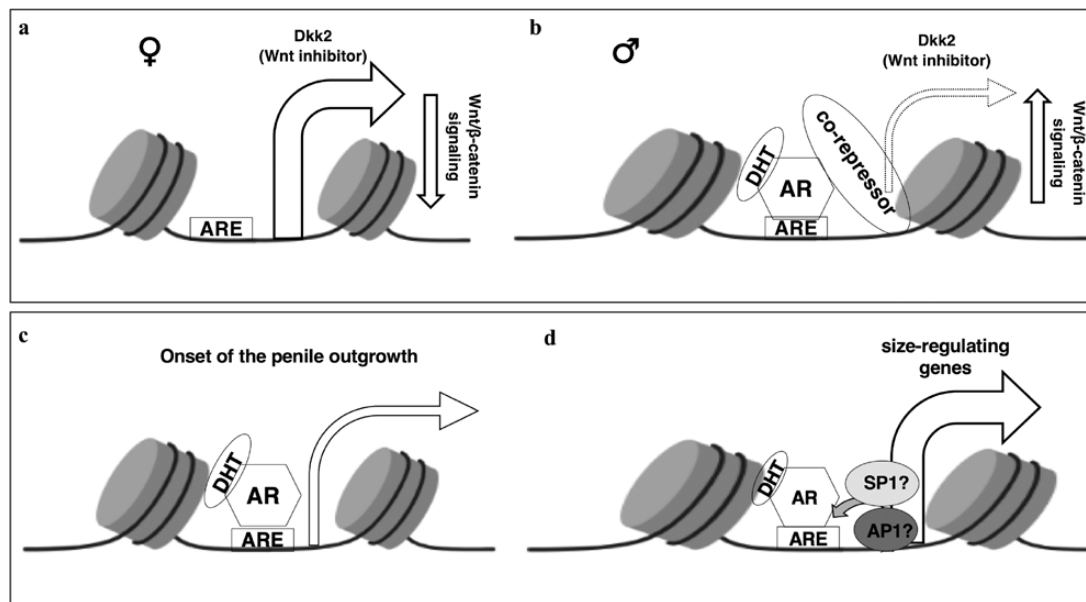


Figure 1. (a-b) A schematic figure of the possible cross talk between androgen and Wnt/ β -catenin signaling for genital tubercle (GT) masculinization in mice. Activation of the Wnt/ β -catenin signaling pathway is necessary for GT masculinization. Dkk2 (Dickkopf-related protein 2), encoding an extracellular antagonist of Wnt/ β -catenin signaling, is regulated negatively by androgens (testosterone and dihydrotestosterone) through the androgen receptor (AR). (a) Dkk2 is highly expressed in female GT mesenchyme. (b) In the male GT, Dkk2 is regulated negatively by AR, permitting the activation of the Wnt/ β -catenin signaling. See Reference 9 for details. Abbreviations: ARE, androgen responsive element; DHT, dihydrotestosterone. (c-d) Epigenetic regulation of murine external genitalia masculinization. (c) Androgen-induced genes that are responsible for masculinization of the external genitalia are regulated by androgen receptor (AR). (d) Housekeeping transcription factor genes, such as Specificity protein 1 (SP1) and Activator protein 1 (AP1) are required as co-factors for modulating histone modifications to promote masculinization. Hence such genes are necessary to regulate the competency of the sexual differentiation of the GT. See Reference 10 and 11 for details. Created with Biorender.com.

maternal use of antifungals [25, 26], as well as a reported association between exposure to endocrine disruptor chemicals and micropenis [27-29]. However, the association between maternal exposure to endocrine disruptors when assessed by measurement of antenatal urinary concentrations of phthalates and related chemicals has not shown this same relationship [30, 31]. Furthermore, the stretched penile length (SPL) in male newborns has not shown a temporal reduction over the last 7 decades (Table 1) [22, 32-57]. Notably, the reports from the United States from the 1970s and most recently in 2021 document a similar SPL [22, 32, 57] as does a study performed in South Korea which compared newborn SPL over 2 temporal periods 25 years apart [41]. This observation of a lack of a temporal association to a change in penile length is contrary to the reports of increasing birth prevalence of other conditions that may be associated with a disruption in androgen exposure, such as hypospadias and cryptorchidism [23, 58].

Identification of Micropenis

Micropenis has to be differentiated from buried, webbed, or trapped penis. In the webbed penile anomaly, the scrotal sac extends onto the ventral aspect of the penile shaft, giving the visual appearance of a small penis, but palpation of the corpora will reveal the true state. In approximately

3% to 4% of newborns, the shaft of the penis may be buried within the peripubic fat [39], and this is commoner in older and particularly overweight boys. A trapped penis refers to a penis that has become entrapped by scar tissues or excessive excision of preputial or shaft skin following an intervention such as a circumcision. Other associated penile malformations include chordee, when the penis is curved, and this can give an impression of a micropenis. It follows that prior to measurement of the penile length, there is a need for a careful examination of the penis and the rest of the genitalia. Penile length should be measured as SPL: the suprapubic fat should be pressed inwards as much as possible, the foreskin must be retracted, and the glans penis should be held with the thumb and forefinger; then, the measurement should be taken from the pubis to the distal tip of the glans penis, over the dorsal side [59, 60]. The SPL that is measured in the newborn within the first 12 hours of life has been reported to be 10% shorter than the true SPL and may thus require re-assessment [39]. The inter- and intra-observer variation for trained personnel has been reported as 1 SD of 0.34 cm and 0.18 cm, respectively [47]. Another measurement technique that has been described uses a modified 10-mL syringe in which the penis is stretched during the suction [61]. It is possible that this method may reduce the measurement variability which is introduced by the suprapubic fat [60] but this requires

Table 1. Summary of studies reporting stretched penile length (SPL, expressed as median or mean and SD) in full-term newborn (except for Reference 44, male infant born at 30-36 weeks of gestation), from a wide range of ethnic backgrounds

Ref	Year	Country	n	SPL (cm)	-2.5 SDS (cm)
[32]	1942	USA	125	3.75	NA
[57]	1975	USA	37	3.5 ± 0.7	2.5
[33]	1987	Japan	25	2.9 ± 0.5	1.4
[43]	1989	Indonesia	336	2.9 ± 0.2	2.4
[44]	1998	Australia	188	(0.16 × GW) -2.27	NA
[45]	2001	Canada	105	3.4 ± 0.3	2.7
[46]	2002	Saudi Arabia	379	3.6 ± 0.57	2.2
[47]	2006	Europe	1962	3.5 ± 0.4	2.5
[48]	2006	Taiwan	156	2.9 ± 0.4	1.9
[36]	2007	Brazil	126	4.7 ± 0.8	2.7
[49]	2007	Mexico	781	2.7 ± 0.5	1.5
[50]	2009	Malaysia	195	3.5 ± 0.4	2.5
[38]	2010	Europe	310	3.6 ± 0.46	2.5
[51]	2014	Nigeria	226	3.4 ± 0.5	2.2
[40]	2014	Japan	1210	3.1 ± 0.26	2.5
[52]	2016	India	1015	3.3 ± 0.38	2.4
[41]	2016	Korea	86	4.1 ± 0.8	2.1
[53]	2017	Turkey	249	3.2 ± 0.55	1.8
[34]	2018	Egypt	37	3.5 ± 0.6	2.0
[42]	2018	China	98	2.8 ± 0.5	1.6
[54]	2018	Iran	203	2.6 ± 0.15	2.2
[55]	2019	Sri Lanka	369	3.0 ± 0.37	2.1
[56]	2020	Europe	174	3.1 ± 0.54	1.8
[22]	2021	USA	197	3.6 ± 0.5	2.4

further study. Since the first report by Schonfeld and Beebe in 1942 [32], several studies have reported normal values of SPL for newborn full-term male infants (Table 1) and pre- and post-pubertal boys, related to age, Tanner stages, and ethnicities [22, 32-36, 38, 40-57]. For Caucasian pre-term infants born at 24 to 36 weeks' gestation, Tuladhar et al proposed that normal values of SPL could be calculated using the formula: $(0.16 \times \text{weeks of gestation}) - 2.27$ [44].

Micropenis is defined as a normally formed penis with a SPL that is less than 2.5 SDS below the mean for the patient's age [59] and ethnicity [45]. In term newborns, micropenis may be defined as a SPL of less than 1.5 cm in Japan and Mexico, 1.8 cm in Europe, and 2.7 cm in Brazil (Table 1). Based on these data, perhaps 2 cm may represent a more appropriate cutoff as an international standard while bearing in mind the regional and genetic differences (Fig. 2). Recently, some studies have also reported measurements of penile circumference for preterm and term neonates [54], but this has not been regularly measured when assessment is undertaken for micropenis.

Etiology

Micropenis may present as an isolated genital condition, it may present with other abnormalities of the genitalia, such as undescended testes, hypospadias, or bifid scrotal folds, or it may be one

of several features of a congenital syndrome with multisystem abnormalities [59]. Endocrine causes of micropenis can be attributed to a defect of the hypothalamic-pituitary-gonadal axis (congenital hypogonadotropic hypogonadism) [62] that may present alone or in combination with inadequate or absent production of other anterior pituitary hormones (congenital hypopituitarism) [63]. Multiple pituitary hormone deficiencies may also be part of a syndromic spectrum, such as Prader-Willi syndrome [64], Bardet-Biedl syndrome [65], Laurence-Moon syndrome [66], Charge syndrome [67], Silver Russel syndrome [68], and Rud syndrome [69]. Micropenis that is present as an isolated feature or present in combination with other urogenital anomalies, may also point toward a wide range of differences/disorders of sex development (DSD) [70]. Moreover, micropenis has been described in many genetic syndromes, including those caused by autosomal or sex chromosomal aneuploidies such as trisomies 8, 13, 18, and 21 or poly-X syndromes, such as Klinefelter syndrome [71] and 49 XXXXY [72] (Table 2). Micropenis can also be a presenting feature of hypogonadism in men; for instance, in Klinefelter syndrome, 10% to 25% of men may have micropenis [73, 74].

The Evaluation of an Infant With Micropenis

Infants with micropenis, isolated or associated with atypical genitalia, need to be considered for clinical, genetic, and

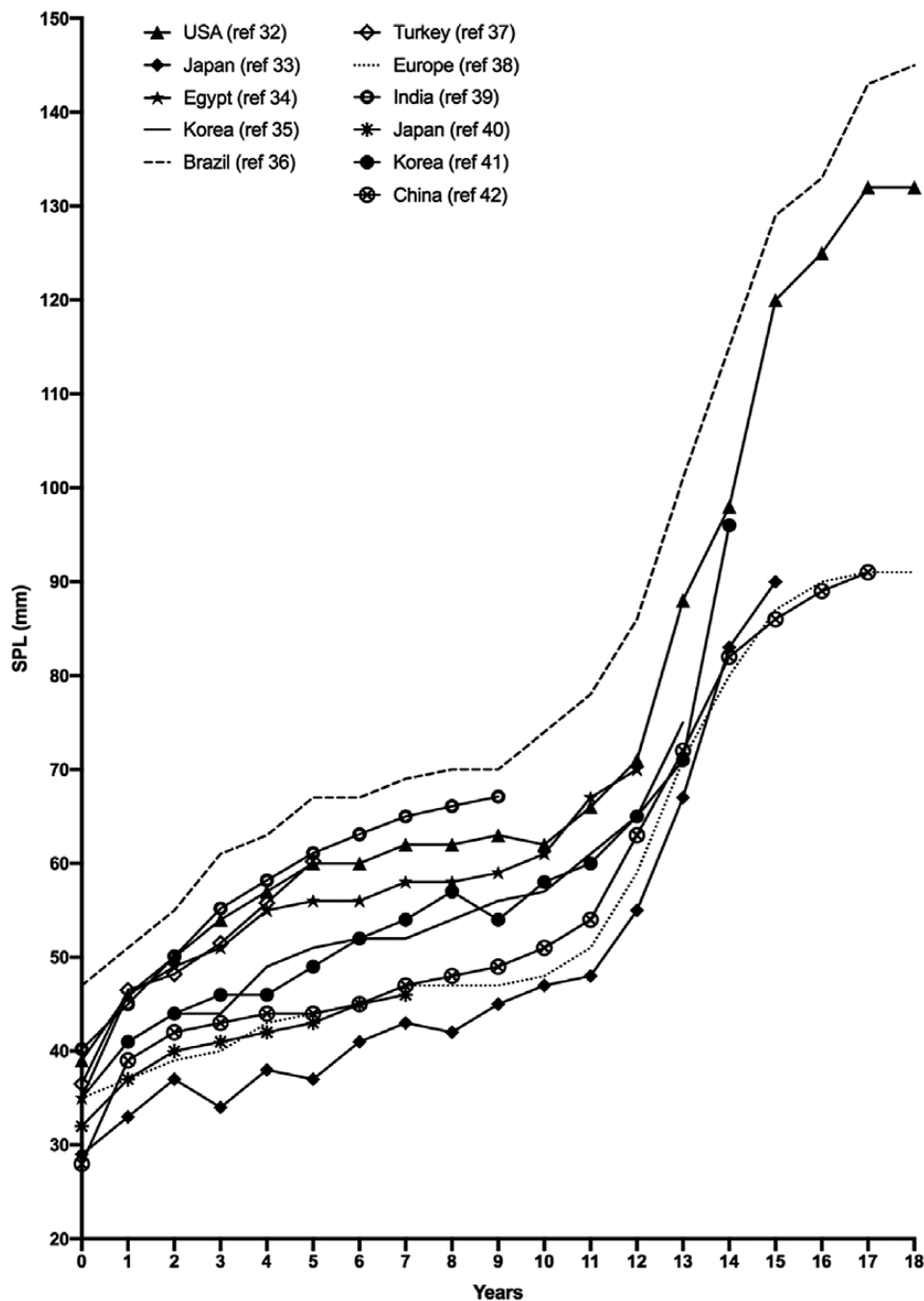


Figure 2. SPL in boys across childhood and adolescence in different ethnic backgrounds. The numbers refer to the bibliographic citation in References and Table 1.

endocrine evaluation by a specialized multidisciplinary team [75]. Although micropenis is instinctively considered to be an exclusively male condition, it is important to bear in mind that 46, XX infants and children with a disorder of androgen excess such as congenital adrenal hyperplasia may present as an apparent boy with micropenis and bilateral undescended testis [76]. In newborn girls, the length of the clitoris does not seem to be dependent on gestation and a newborn with a clitoral length greater than 8 mm requires further evaluation

[60]. Micropenis, isolated or combined with other urogenital anomalies (hypospadias, undescended testes, malformation of the scrotum) may be related to a range of endocrine disorders and differential diagnosis may be really challenging. The coexistence of neonatal metabolic or neurological anomalies (such as neonatal hypoglycemia, prolonged jaundice, hypotonia) and/or dysmorphic features needs to be considered to exclude concomitant absent production of other anterior pituitary hormones (congenital hypopituitarism)

Table 2. Conditions Associated with Micropenis

Hypogonadotropic hypogonadism
Isolated
Combined with other pituitary hormone deficiency (hypopituitarism)
Syndromic conditions:
• Prader-Willi syndrome
• Bardet-Biedl syndrome
• Laurence-Moon syndrome
• Charge syndrome
• Silver Russel syndrome
• Rud syndrome
Hypergonadotropic hypogonadism
Congenital anorchia
Klinefelter syndrome and other X chromosome aneuploidies
Disorders of gonadal development:
• Sex chromosome mosaicism
• Partial gonadal dysgenesis
Syndromic conditions, eg:
• Down syndrome
• Prader-Willi syndrome
• Bardet-Biedl syndrome
• Laurence-Moon syndrome
Disorders of androgen synthesis
3-beta-hydroxysteroid dehydrogenase deficiency
17-beta-hydroxysteroid dehydrogenase deficiency
17,20-lyase deficiency isolated or combined with 17- α -hydroxylase deficiency
5- α -reductase deficiency
Disorders of androgen action
Partial androgen insensitivity syndrome
Growth hormone deficiency
Penile agenesis (aphallia)
Maternal use of antifungals
Environmental endocrine disruptors
Nonspecific 46 XY DSD or idiopathic micropenis (ie, cases that do not have any evidence of endocrine or genetic abnormalities)

and/or syndromic diseases, mentioned above. In boys with micropenis with additional concerns about short stature or growth retardation, the threshold for evaluating the growth hormone axis should be lowered. Given that the etiology of micropenis includes a wide range of conditions associated with DSD, children with isolated micropenis who do not have hypogonadotropic hypogonadism (HH), isolated or combined with other anterior pituitary hormone deficiencies, should also undergo a careful evaluation for DSD [75]. When congenital hypogonadotropic hypogonadism (CHH) is suspected, measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone in early infancy and especially between 1 and 3 months of age may be helpful to catch the minipuberty surge, before these hormones decline until the beginning of puberty [77]. However, low concentrations of gonadotropins or sex steroids have

little diagnostic utility and need to be followed by dynamic stimulation tests including a luteinizing hormone–releasing hormone (LHRH) stimulation test and a hCG stimulation test. The results of these dynamic tests in boys with possible CHH need to be interpreted carefully as a normal LHRH stimulation test may not necessarily exclude CHH [78] and a poor testosterone rise following hCG stimulation is not uncommon in CHH [79]. It is possible that a more prolonged hCG test, consisting of the standard hCG test followed by further 2 injections per week for the following 2 weeks, with blood sample collected the day after the last injection, may be more appropriate in such cases but this requires further study [80]. Serum anti-Müllerian hormone (AMH) and inhibin B are also likely to be low in those with CHH [81] but given that they may also be low in disorders of gonadal development, the results need to be interpreted in combination with the results of the other endocrine investigations. The additional clinical utility of INSL3 as a biochemical marker of hypogonadotropic hypogonadism requires further exploration [82].

In cases that are suspected to have a DSD, abdomen ultrasound or magnetic resonance imaging are useful for detecting the Müllerian structures and to visualize the testes in case of abdominal cryptorchidism [83]. However, these tools are operator dependent and may also depend on the state of the child and the results need to be interpreted cautiously and in combination with the results of the other investigations. Magnetic resonance imaging of the brain, including the pituitary and the olfactory tracts, should be performed in cases of suspected hypogonadotropic hypogonadism [84, 85]. Increasingly, diagnostic genetics utilize high-throughput sequencing or whole exome/genome sequencing for analyzing panels of candidate genes and given the wide range of causes of micropenis, detailed molecular genetic analysis will be guided by the results of the clinical evaluation and may require a panel that includes genes that are implicated in DSD and hypogonadotropic hypogonadism. Molecular genetic analysis should be accompanied by a microarray to identify copy number variation especially in those cases where there are associated extragenital features [86]. In centers with greater access to high-throughput sequencing or whole exome/genome sequencing, it is possible that in the diagnostic pathway, genetic testing may be performed at an earlier stage than the more physically demanding dynamic endocrine investigations mentioned above. It is also increasingly becoming clear that even some of the screening tests, such as AMH and inhibin B, may be normal in genetically confirmed cases of CHH [87]. Thus, the clinician may need to consider having a very low threshold for genetic investigation in cases of isolated micropenis.

Table 3. The effect of testosterone treatment on stretched penile length (Δ SPL)

	Age	n	Condition	SPL before treatment (SDS)	T treatment	Δ SPL (SDS)
Guthrie et al. 1973	34 mo	4	Prader-Willi		T cypionate 25 mg every 3 weeks for 3 months	1.8-3.5 cm
	12 mo		Prader-Willi			
	21 mo		NS syndrome			
	6 mo		NS-DSD			
Velasquez et al. 1998	0.7 \pm 1 mo	13	Micropenis	-4.6 \pm 1.0	4-8 injections of T heptylate (100 mg/m ²) every 2 weeks	2.8 \pm 0.7
	7.6 \pm 1.5 mo			-2.5 \pm 1.0		1.5 \pm 0.2
	4.5 \pm 2.5 y			-3 \pm 1.0		2.3 \pm 1.0
	0.4 \pm 0.5 mo			-4.0 \pm 2.0		1.9 \pm 1.2
	7.6 \pm 5 mo			-2.5 \pm 0.0		0.8 \pm 0.8
	5 \pm 3.5 y			-3.0 \pm 0.0		0.5 \pm 0.2
Bin-Abbas et al. 1999	4 mo to 2 y	4	HH	-4	T enanthate 25-50 mg every 4 weeks for 3-6 months	2.4
	6-13 y			-3.4		2
Arisaka et al. 2001	5 mo to 8 y	50	NS-DSD	18.9 \pm 4.4 mm	T cream 5% 10 mg daily for 30 days	8.4 \pm 0.7 mm
Zenaty et al. 2006	0.7 \pm 0.5 y	19	Bilateral anorchia	-2.8 \pm 0.8	3-4 injections of T heptylate (50-150 mg/m ²) every 2-4 weeks	1.9 \pm 1.3
Ishii et al. 2010	2.6 \pm 1.8 y	19	Micropenis	-3.0 \pm 0.8	T enanthate 25 mg every 4 weeks up to 3 times	1.4 \pm 0.7
	1.4 \pm 1.3 y			0.8 \pm 0.6		0.9 \pm 0.6

Abbreviations: HH, hypogonadotropic hypogonadism; NS-DSD, nonspecific differences/disorders of sexual development; NS syndrome, nonspecific syndrome; SDS, standard deviation score; SPL, stretched penile length; T, testosterone

Hormonal Management of Micropenis

The main goal of treatment in boys with micropenis has usually been based on increasing the penile length with an assumption that it leads to an increase in self-esteem and body image of the boy while reassuring the parents of the newborn infant. In those cases that are suspected to have a DSD, this form of therapy may also allow the capacity to assess androgen responsiveness. Therapy with sex hormones can be broadly divided into androgen therapy or gonadotropin therapy and establishing the etiology of micropenis would be helpful before therapy is envisaged. While several reports exist on androgen and gonadotropin therapy for micropenis and these will be discussed in more detail later, there remains a paucity of evidence for their long-term efficacy in improving SPL. A recent report suggested that irrespective of the severity of the micropenis and whether hormonal therapy is administered or not, in those with normal gonadal function, SPL shows an increase at puberty and this improvement is greatest in those with shortest age-matched SPL [88]. In those where the micropenis is associated with an endocrine disorder, the results on long-term outcome are quite mixed, with one study reporting that long-term SPL may not show an increase despite early-stage hormone therapy [89] and another showing an increase in SPL in response to hormone therapy during puberty [5].

Testosterone Therapy

Short-term use of intramuscular administration of testosterone esters has been reported often [90-94] (Table 3). Adverse effects have rarely been described and may include a temporary acceleration in growth rate with a transient advance in bone age maturation, but any effect on final height has not been reported [90]. There are no standard guidelines or consensus on the dosage, method of administration, or duration of testosterone therapy in boys with micropenis. Since the 1970s, several studies have reported a regimen of intramuscular depot-testosterone 25 mg, administered monthly, in one or two 3-month courses [90, 92, 94, 95]. This regimen of testosterone enanthate 25 mg every 4 weeks has been reported to show an increase in penile length of over 100% in prepubertal boys with CHH [92], anorchia [93], isolated micropenis [95], and hypospadias with no demonstrable *AR* or *SRD5A2* variants [94]. Arisaka et al also documented a significant increase in SPL in 50 prepubertal boys treated with testosterone cream 5% (10 mg/daily applied directly to the phallus) for a duration of 30 days. In this study, the boys had an age range between 5 months and 8 years and the increase in SPL was noticed to be greater in those who were older. Transdermal testosterone was also associated with a rise in plasma levels

of testosterone and insulin-like growth factor 1, although there was no rise in plasma osteocalcin as a marker of bone formation [96]. There is a need to understand the optimal age of therapy for maximal effect [97, 98] as this may be related to the period when there is maximal androgen sensitivity perhaps based on maximal tissue expression of *AR* [99]. Given that tissue *AR* expression is high in early infancy, it would seem appropriate to use androgens at that point, but it remains unclear whether such early use of androgens has any benefit on penile length in adulthood [100-102] (Table 3). Studies in rats with micropenis suggest that therapy at an early stage may be less effective in promoting penile growth than at an age that would be equivalent to puberty [98]. More recently, testosterone therapy has also been described for the management of scrotal hypoplasia in young children [103].

Topical Dihydrotestosterone Gel Treatment

The effect of topical administration of dihydrotestosterone (DHT), the nonaromatizable form of testosterone, in undervirilized children with 5α -reductase deficiency, was first described in 1990 by Carpenter et al [104]. Since then, the use of DHT 2.5% gel has been reported in several studies, as an alternative to intramuscular testosterone, especially in boys with partial androgen insensitivity syndrome (PAIS) or 5α -reductase deficiency [104-111] (Table 4). Although high-dose intramuscular testosterone may promote the virilization of the external genitalia in these conditions [112], there is a risk that aromatization of the high levels of circulating testosterone may lead to a premature growth spurt, precocious puberty, bone age advance, and pronounced gynecomastia [113, 114]. On the other hand, the supply of DHT gel has often been erratic and there is also a risk of cross-contamination of close contacts (especially children and women) if patients do not follow application instructions [115]. As for testosterone therapy, there are no standardized guidelines or consensus on therapeutic regimen for DHT transdermal gel application to genital skin. The majority of studies that have reported a clear effect on SPL have used a daily dose of 12.5 mg in boys < 10 years of age and 25 mg in boys \geq 10 years of age, for 4 to 16 weeks [105, 109]. Charmandari et al documented a significant increase in SPL at a lower dose of 0.2 to 0.3 mg/kg/daily, for 3 to 4 months [106]. Adverse effects that have been documented include a transient decrease of high-density lipoprotein cholesterol to total cholesterol ratio and increase of alkaline phosphatase [105]; patients may also experience a rash and an itch of the genital skin [105]. A more detailed investigation of other wider effects of DHT such as that on hematocrit have not been investigated. The clinical response in SPL to DHT treatment can

Table 4. The effect of dihydrotestosterone treatment on stretched penile length (Δ SPL)

	Age	n	Diagnosis	SPL before treatment	DHT treatment	Δ SPL	
Carpenter et al. 1990	9 mo	1	SRD5A2 def	1.8 cm	2% DHT cream, 2.5 mg/daily, for 4 mo	2 cm	
Odame et al. 1992	6 y	1	SRD5A2 def	2.5 cm	2.5% DHT gel, 2.5 gr twice daily for 3 mo	2 cm	
	9 mo	1	SRD5A2 def	0.5 cm	2.5% DHT gel, 2.5 gr twice daily for 6 mo	2.1 cm	
Choi et al. 1993	3-15 y	22		<2 SDS	<10 y: 2.5% DHT gel 12.5 mg/daily for 8 weeks >10 y: 2.5% DHT gel 25 mg/daily for 8 weeks	First 4 weeks: +153 \pm 17% Second 4 weeks: 118 \pm 13%	
			13 NS-DSD				
			3 PAIS				
			2 HH				
			2 DAS 2 GHD				
Charmandari et al. 2001	8.3 y 1.9 y 3-0 y 7.8 y 2.0 y 7.6 y	6	SRD5A2 def	<2.5 SDS	2.5% DHT gel, 0.15-0.33 mg/Kg/daily, for 2.5-4 mo (<3 y: 2.5 mg/daily) (>3 y: 5.0 mg/daily)	1.1 cm 0.5 cm 2 cm 2 cm 1.5 cm no response	
			Robinow syndrome				
			Buried micropenis				
			Buried micropenis				
			Micropenis, hypospadias				
			Micropenis				
Bertelloni et al. 2007	NA NA 2 mo	3	SRD5A2 def	1.5 cm 1.2 cm 1.6 cm	2.5% DHT gel, 2.5 gr twice daily for 3-6 mo	1.6 cm 1.8 cm 2.3 cm	
Becker et al. 2015	24 y 13 y 11 y	3	PAIS	6.1 cm 3.5 cm 2.5 cm	2.5% DHT gel, 0.3 mg/Kg/daily for 4 mo	no response 2.2 cm 1 cm	
Xu et al. 2016	4.1 \pm 3.4 y	23		1.68 \pm 0.6 cm	2.5% DHT gel, 0.1-0.3 mg/Kg/daily for 3-6 mo	After 3 mo, 22 pt: -0.11 \pm 0.45 cm After 6 mo, 15 pt: -0.22 \pm 0.43 cm	
			16 NS-DSD 5 SRD5A2 def 2 PAIS				
Sasaki et al 2019	11 y 10.5 y 8 y 4 y	4	SRD5A2 def	-1.9 -3.1 -2.3 -2.7	2.5% DHT gel, 12.5-25 mg/daily, for 8-16 weeks	1.2 cm [1.5 SDS] 2.8 cm [3.4 SDS] 1.4 cm [2.3 SDS] 1.5 cm [2.2 SDS]	

Abbreviations: DAS, disorders of androgen synthesis; DHT, dihydrotestosterone; GHD: growth hormone deficiency; HH, hypogonadotropic hypogonadism; NA, not available; NS-DSD, nonspecific differences/disorders of sexual development; PAIS, partial androgen insensitivity syndrome; SDS, standard deviation score; SPL, stretched penile length; SRD5A2 def, 5 α -reductase-2 deficiency; T, testosterone.

be variable, depending on the underlying diagnosis and the age of therapy; in those with PAIS, response to DHT may vary according to the specific AR variant [107, 116]. In clinical practice, an increase in SPL has been reported in PAIS [107] and 5 α -reductase deficiency [109] in pre- and peripubertal patients but not in adults. However, the response in cases of 5 α -reductase deficiency has not been as marked as expected [109]. It has been proposed that DHT may play an important role on AR expression, promoting synthesis and repressing degradation [109, 117]; for this reason, intracellular DHT deficiency could reduce androgen sensitivity in DHT-dependent tissues [109, 118], explaining the limited effect of exogenous DHT in 5 α -reductase deficiency.

Gonadotropin Treatment

The first report of micropenis treatment with hCG dates back to 1993, when Almaguer et al described notable penile growth in 6 neonates after 3 hCG intramuscular injections [119]. Subsequently, treatment with recombinant gonadotropins was proposed as an alternative treatment to testosterone in male infants and peripubertal boys with CHH, as a treatment that would mimic the physiological activation of hypothalamic-pituitary gonadal axis [120]. In 2002, Main et al first reported treatment with recombinant gonadotropins in an infant diagnosed with CHH [121]. Therapy consisted of recombinant LH (20–40 IU) and FSH (21.3 IU) twice weekly for approximately 7 months and was successful in improving penile length, while inducing testicular growth and mimicking physiological minipuberty [121]. Further studies have reported the effectiveness of gonadotropin treatment in increasing SPL in boys with CHH during the first year of life [120, 122–124]. Bougneres et al described the continuous infusion of gonadotropins with an insulin pump in 2 neonates with micropenis and CHH [123]. Patient 1 began continuous subcutaneous infusion at 8 weeks (rhLH 56 IU and rhFSH 67 IU daily) until 25 weeks of life; patient 2 started continuous subcutaneous infusion at 20 weeks (rhLH 50 IU and rhFSH 125 IU daily) until 48 weeks of life. SPL increased from 8 to 30 mm in patient 1 and from 12 mm to 48 mm in patient 2, with a concomitant increase in testicular volume and serum testosterone, inhibin B, and AMH in both neonates [123]. However, in general, reports of gonadotropin treatment during the neonatal and infant period are still limited. Given the respective differences in the half-life of hCG and LH [121], there is a need for further comparison of the relative efficacy of these 2 drugs. In addition, further long-term studies are required to explore outcomes such as fertility [62] (Table 5).

Surgical Management of Micropenis

In 1996, Wessels et al provided guidelines for penile elongation, suggesting that only men with a flaccid length of less than 4 cm or a SPL of less than 7.5 cm should be considered for surgical treatment [125]. Since the first reconstructive intervention, reported by Hinman in the early 1970s [126], several surgical techniques have been developed [127]. However, the role of surgery in the management of micropenis is limited, with multiple techniques described with little in the way of high-quality evidence to guide the clinician. Surgery is only performed in adulthood and is reserved for the most extreme cases. The surgical options can be divided into techniques that lengthen the penis, options to augment the girth of the penis, surgery to make the penis appear larger, and replacement of the phallus altogether. To increase penile length, the suspensory ligament can be released, and this can be performed in conjunction with a V-Y dorsal incision [128–130]. Other techniques, such as the sliding elongation [131, 132] and penile disassembly [133], have been described. The increase in penile length is small (1–3 cm) [127] and subsequent scarring can cause retraction and a reduction in length. There can also be problems with erectile function and stability of the penis, which can affect sexual function. The girth of the penis can be increased by the injection of substances around the shaft of the penis: hyaluronic acid, liquid silicone, polyacrylamide, and autologous fat have been tried, with limited success. The main issue has been reabsorption of the substances injected or the precipitation of scarring that affects function or causes retraction of the penis [134–136]. The perceived length of the penis can be increased with removal of suprapubic fat. This can be attempted with weight reduction measures but can also be augmented with removal of suprapubic fat using liposuction or more radical surgery [137]. The penis itself can also be replaced with an augmentation phalloplasty and many techniques have been described so far [138]. Currently, a radial artery-based forearm free flap is employed with reasonable cosmetic outcomes and acceptable donor complications [139]. However, despite the evolution of these techniques, they cannot replicate the normal anatomy and function of the penis and clearly further research is needed to identify the best surgical procedure, in terms of which intervention will provide the highest long-term patient satisfaction and the lowest likelihood of postoperative complications.

Psychosocial Outcomes

Although men with micropenis may have normal experience of sexual pleasure and orgasm [140–142], sexual dissatisfaction has also been reported: having a micropenis has been reported to have a negative impact on sexual self-confidence, leading to social or sexual avoidance

Table 5. The effect of gonadotropin treatment on stretched penile length (Δ SPL)

Author	Year	Age	n	Diagnosis	SPL before treatment	Treatment	Δ SPL
Almaguer et al.	1993	Neonates	6	NS-DSD	8-20 mm	hCG 1500 IU \times 3 days	0.25-0.75 cm
Main et al.	2002	7.9-9.6 mo	1	HH	16 mm	rhLH 20 IU + rhFSH 21.3 IU \times 2/week	8 mm
		9.6-11.3 mo				rhLH 40 IU + rhFSH 21.3 IU \times 2/week	11 mm
		12.2-13.7 mo				rhFSH 21.3 IU \times 2/week + T suppositories 1 mg/day	
Bougneres et al.	2008	8 wk	1	Hypopituitarism	8 mm	CSI: 56 IU rhLH + 67 IU rhFSH/daily, for 17 weeks	13 mm
		20 wk	1	HH	12 mm	CSI: 50 IU rhLH + 12.5 IU rhFSH/daily, for 28 weeks	36 mm
Kim et al.	2011	18.9 \pm 2.2 y	20	HH	5.1 \pm 1.9	hCG im 1500-2000 IU \times 3/week, for 8 weeks	2 \pm 1.7 cm
Stoupa et al.	2016	1.5 mo	1	PAIS	13 mm	CSI: 75-225 IU rhLH + 75 IU rhFSH/daily, for 3-6 mo	25 mm
		5.5 mo	1	Hypopituitarism	15 mm		30 mm
		4.5 mo	4	HH	6 mm		32 mm
		4.5 mo			15 mm		20 mm
		3.0 mo			20 mm		28 mm
		3.5 mo		11 mm	34 mm		
Kohva et al.	2019	4.2 mo	1	Chargé syndrome	14 mm	rhFSH sc 7.5-16.7 IU \times 2-3/week, for 3-4.5 mo + T enanthate 25 mg every 4 weeks, for 3 mo	17 mm
			4	Hypopituitarism			
		0.7 mo			10 mm		14 mm
		3.1 mo			15 mm		9 mm
		1.3 mo		24 mm	11 mm		
		3.3 mo		23 mm	7 mm		

Abbreviations: CSI, continuous subcutaneous infusion; DHT, dihydrotestosterone; hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; NA, not available; NS, nonspecific; NS-DSD, nonspecific differences/disorders of sexual development; PAIS, partial androgen insensitivity syndrome; rhFSH, recombinant human follicle-stimulating hormone; rhLH, recombinant human luteinizing hormone; SDS, standard deviation score; SPL, stretched penile length; T, testosterone.

[143-145]. It is a matter of concern that, even after hormonal or surgical treatment in childhood and/or adolescent age, a different genital appearance may contribute to poor self-esteem, social anxiety, and reduced quality of life [146, 147]. Whether or not a clear correlation exists between penile dimensions and sexual dysfunction and long-term quality of life remains unclear, as the majority of studies have not used standardized and validated instruments [3]. In addition, counseling of the parents of affected boys and active involvement of the partners of affected men may be associated with better outcomes [3], in terms of achieving greater self and social acceptance of the condition. Thus, psychological counseling and long-term psychological support should be provided with an age-appropriate explanation of the diagnosis. The availability of psychological support is known to be particularly low for adults with conditions affecting sex development [148] and those who do provide this support should also have links to experts in sex therapy, in case this is required.

Conclusion and Future Directions

In summary, micropenis needs a multidisciplinary approach for its assessment, management, and treatment so that an individualized plan can be made for each patient. There is a lack of systematic studies comparing the impact of the wide range of hormone therapies that are available on long-term outcomes, including quality of life and sexual satisfaction. To date, research has been hampered by a small sample size and heterogeneous diagnoses and assessment tools. There is a need for a greater collaborative effort in collecting standardized data so that all real-world or experimental interventions performed at an early age can be studied systematically into adulthood.

Additional Information

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