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Enhancement Risk Disease Cardiovascular in Children with Hypospadias

Aulia Wiratama Putra[1*], Yoga Eka Prayuda[2], Levita Dyah Kartika Suherman[3], Tiffani Ratu[4], Ari Harto Cahyono[5]

[1] Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[2] Faculty of Medicine, UIN Jakarta, Indonesia
[3] Faculty of Medicine, Universitas Airlangga, Indonesia
[4] Faculty of Medicine, Universitas Kristen Indonesia, Indonesia
[5] Faculty of Medicine, Universitas Diponegoro, Indonesia

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Corresponding Author:

Aulia Wiratama Putra
Faculty of Medicine,
Universitas Trisakti, Jakarta,
Indonesia
Email: whiratama@gmail.com

ABSTRACT

Hypospadias is a congenital disorder in boys due to low fetal androgen hormones. Hypospadias is one of the congenital disorders with the highest prevalence. Several studies have revealed the association of hypospadias with cardiovascular disease. There are still very few studies that summarize cardiovascular manifestations in pediatric hypospadias. Therefore, this study was designed to describe the cardiovascular risk in pediatric patients with hypospadias. Method: Journal searches were carried out through several research databases including Google Scholar, PubMed, and Sciencedirect . The keywords used were "hypospadias", "cardiovascular", and "pediatric". The results of the literature search were 1,543 journals with 20 journals meeting the criteria. Results and Discussion: Hypospadias is one of the second most common congenital abnormalities in men after testicular undescensus . Children born with hypospadias are proven to experience changes in vascular structure, namely increased carotid intima media thickness (CMIT) and are associated with hypertension. Hypospadias patients have impaired endothelial function, decreased vasorelaxation, and increased vasoreactivity. The underlying mechanism is a Rho kinase and ROS dependent process. Conclusion: Children with hypospadias have a higher risk of cardiovascular disease.

Keywords:

Hypospadias, Cardiovascular, Pediatric

1. INTRODUCTION

Hypospadias is a congenital disorder in boys due to low levels of fetal androgen hormones. This disorder is defined as a malformation from the ectopic placement of the urethral orifice in the ventral, distal to proximal part of the penis [1]. Hypospadias is one of the congenital abnormalities with the highest prevalence. Although surgical intervention can be performed to repair the urogenital structure, children with hypospadias have been associated with ongoing psychosocial, psychosexual and functional disorders. 2 Hypospadias has a complex etiology and depends on the underlying biological mechanisms [2]. This mechanism can be associated with many other malformations, especially cryptorchidism [3]. Because testosterone and dihydrotestosterone (DHT) affect the development of male external genitalia, the etiology of hypospadias is thought to often be caused by disturbances in fetal androgens due to genetic mutations. Environmental risk factors for hypospadias are related to intrauterine growth restriction [4]. It is hypothesized that impaired placental function may also lead to reduced androgen effects through decreased production of human chorionic gonadotropin (hCG) [5].

Several studies have revealed the association of hypospadias with cardiovascular disease. Hypogonadism in hypospadias has been identified as an independent determinant of increased risk of endothelial dysfunction in men. 5 A growing body of evidence has demonstrated an association between hypospadias in adult men and secondary morbidity and mortality from cardiovascular disease [6]. 4 Clinical studies have demonstrated an association between

hypogonadism in adult men and morbidity and mortality. due to cardiovascular disease, which is the leading cause of death worldwide [7]. The molecular and cellular mechanisms by which testosterone deficiency/hypogonadism affects vascular function are very complex and involve many androgen-sensitive signaling pathways [8]. However, to date there are very few studies that summarize the cardiovascular manifestations in pediatric hypospadias. Therefore, this study was designed to describe the cardiovascular risk in pediatric patients with hypospadias [9].

2. METHODS

Writing the manuscript begins with searching, selecting and selecting journals related to the risk of cardiovascular disease in pediatric groups with hypospadias. Journal searches were carried out through several research databases including Google Scholar, PubMed, and Sciencedirect. The keywords used were "hypospadias", "cardiovascular", and "pediatric" [10]. The results of the literature search were 1,543 journals with 20 journals meeting the criteria. We prioritized research published within the last ten years. Writing begins with literature selection through title and abstract, followed by reviewing the contents of each piece of literature that meets the criteria and is followed by discussion between authors. Studies that were not fully accessible were excluded. The final results will be obtained from the studies that will be used in this literature review [11].

3. RESULTS AND DISCUSSION

Hypospadias

Hypospadias is one of the second most common congenital abnormalities in men after undescended testicles. 7 This condition is usually characterized by proximal displacement of the urethral opening, curvature of the penis, and lack of ventral foreskin. Hypospadias occurs due to incomplete closure of the penile structures during embryogenesis so that the urethral opening is shifted along the ventral side of the penis [12]. In approximately 70% of children with hypospadias, the urethral meatus is located distal to the penile shaft, this is considered a mild form that is not associated with other urogenital abnormalities [4]. The remaining 30% are proximal and often more complex.8 In the final consensus regarding the definition of disorders of sexual development, hypospadias is included as one of the forms of disorders of sexual development 46,XY. Many disorders of sexual development have genetic causes, and a number of genes are widely implicated in hypospadias. Only 30% of hypospadias cases have a clear genetic cause, it is thought that a combination of environmental influences and genetic susceptibility causes this anomaly.9 Most hypospadias occurs as an isolated condition, but is associated with several anomalies such as unilateral cryptochidism and micropenis [8]. This condition indicates a hormonal deficiency during embryogenesis [13]. Androgens and estrogens both play important roles in genital development, and if an imbalance occurs, different entities can be seen in the spectrum of congenital penile anomalies such as hypospadias, micropenis, and ambiguous genitalia.8

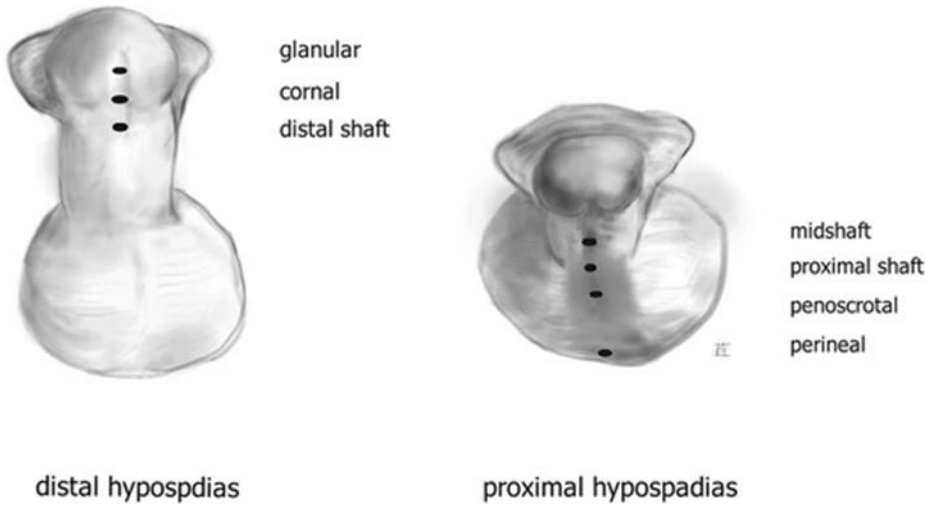

Figure 1. Standard classification of hypospadias

As is universally recommended for hypospadias, circumcision should be delayed, although evidence suggests that surgical outcomes have no significant difference in circumcised penises with distal hypospadias using tubularized incised plate (TIP) repair. In cases of proximal hypospadias associated with unilateral or bilateral non-palpable cryptorchidism, abnormalities of sexual differentiation occur in 17-29% of patients [14]. Therefore, initial evaluation should include serum electrolytes, 17-hydroxyprogesterone (17-OHP), karyotype, abdominal ultrasound to assess Mullerian structures, and endocrine [15]. 10 Surgical intervention for hypospadias can be performed at any age, but most studies recommend intervention surgery at 6-18 months of age [16] The American Academy of Pediatrics recommends this time interval to limit the psychological stress and behavioral problems seen in toddlers undergoing genital surgery [17]. The surgical steps of hypospadias surgery include penile degloving, correction of ventral

curvature (orthoplasty), reconstruction of the urethra (urethroplasty), providing vascular coverage for urethroplasty, reconstruction of the glans (glansplasty), and finally cosmetic skin coverage to create the appearance of a circumcised penis [18].

Increased Risk of Cardiovascular Disease in Children with Hypospadias

Based on research by Herald et al, it was found that children born with hypospadias were proven to experience changes in vascular structure, namely increased carotid intima media thickness (CMIT) and was associated with hypertension [19]. This was caused by inadequate exposure to androgens during the antenatal period of children with hypospadias. This inadequate level is believed to have pathophysiological effects that affect vascular function and increase blood pressure [20].

Another mechanism proposed by Herald et al is that there is damage to small arteries in hypospadias patients. The small arteries of the human body play an important role in total peripheral resistance and blood pressure regulation. In this study, researchers assessed small arteries in the penile tissue of children with hypospadias, which were examined using direct myography to assess vasoreactivity [21]. The results of this examination showed that there were differences in vasoconstriction and vasodilation in hypospadias patients and controls. Hypospadias patients result in impaired endothelial function, decreased vasorelaxation, and increased vasoreactivity. These results indicate abnormal vascular function and involve Rho kinase and ROS dependent processes . The activity of Rho kinase will regulate vascular function of smooth muscle and increase myosin light chain (MLC) phosphorylation through inhibition of MLC phosphatase, this mechanism is believed to be implicated in the occurrence of cardiovascular and urogenital disorders. 6 This increased MLC phosphorylation is associated with the RhoA/Rho kinase pathway and increased Ca2+ channels without amplification of Ca2+ transients. These findings suggest that Rho kinase independently influences MLC sensitivity to Ca 2+ changes, which may contribute to hypercontractility in hypospadias. High ROS is closely related to cardiovascular dysfunction and hypertension. Increased ROS is associated with decreased testosterone levels in men. The exact cause of oxidative stress in conditions of low testosterone is still unclear but may be related to reduced activity of S-nitrosoglutathione reductase, a process that is independent of androgen receptors, sirtuins, and changes in the antioxidant system [22].

According to Phillips et al, patients born with hypospadias are at risk of metabolic and cardiovascular disease, the underlying mechanism of which is the reduced effect of testosterone in men with hypospadias.4 A small number of men born with hypospadias are known to continue to experience hypoandrogenism throughout life due to certain genetic causes. , and this will affect adolescence or adulthood [10]. Several studies have shown that men with hypospadias overall have lower testosterone levels and higher luteinizing hormone (LH) levels compared with controls, indicating reduced testicular testosterone production. Testosterone has important effects on the cardiovascular system [23]. Decreased testosterone levels increase the risk of developing coronary artery disease, metabolic syndrome, and type 2 diabetes. 12 The relationship between low testosterone levels and chronic heart failure has been investigated by several studies and the consensus is that testosterone deficiency is common in patients with chronic heart failure. Testosterone levels in men with chronic heart failure correlate with clinical parameters including ejection fraction, activity capacity, New York Association class (NYHA class), and patient prognosis [24].

Coronary heart disease was found to be associated with low testosterone hormone levels. Based on research conducted by Alkamel et al, it was found that patients with low testosterone experienced premature coronary heart disease compared to controls. 15 Low testosterone increases the risk of increased CMIT and atherosclerosis so that the risk of premature coronary heart disease increases [25]. The research results illustrate that the lower the testosterone level, the more severe the degree of coronary heart disease and blood vessels affected. 15 Testosterone deficiency can worsen coronary heart disease by having a negative impact on components of the metabolic syndrome, such as insulin resistance, hypertension, dyslipidemia, and visceral obesity [26].

In addition to increasing cardiovascular risk, children born with hypospadias have a higher prevalence of suffering from congenital heart disease (CHD) compared to children without hypospadias. Based on research by Richard el al, boys born with hypospadias have a 6 times greater risk of developing major CHD. This may occur due to defects that arise due to disruption of complex embryological pathways [27]. The developmental etiology of similar urogenital and cardiac anomalies is now being investigated in molecular studies. In an animal study of single-gene CHD, 29.8% of variant lines showed renal anomalies [28]. In addition, this study found that 30% of hospitalized CHD patients showed renal abnormalities on imaging, which together supports a common etiology between these systems. 17,18 Genetic studies in children with CHD revealed a complex architecture that includes single gene disorders and polygenic inheritance [12]. In contrast, little is known about the genetic etiology of hypospadias.19 Approximately 70% of hypospadias cases occur outside of known genetic syndromes and their origins are incomplete [29] Many genetic syndromes that include hypospadias also include CHD, including Mowat-Wilson syndrome, Opitz G/BBB syndrome and Wolf-Hirschhorn syndrome [30].

4. CONCLUSION

Children with hypospadias have a higher risk of cardiovascular disease. Some of the underlying mechanisms are early vascular dysfunction including hypercontractility and impaired vasodilation secondary to increased Rho kinase activation and oxidative stress. This manifests later in life as vascular remodeling and increased systolic blood pressure

in adolescence, with an increased risk of hospital admission for cardiovascular disease in adulthood. Babies born with hypospadias also have a 6 times greater risk of major CHD.

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