

Adult Patients with Aphallia: Were they Fertile?

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Abstract: Adult male genotype and phenotype with aphallia are men born without a penis. The effectiveness of male sex assignment or female sex reassignment as a treatment for aphallia has been debated. The study's goal was to address the gonadal existence and supporting investigation related to the reproductive health care of reported cases of aphallia patients such as karyotyping, physical examination, semen analysis, hormone reproduction level, sperm retrieval, radiological investigation type of intervention. In this narrative review, data were obtained from Pubmed and Google Scholar that contains keywords "absence penis", "penile agenesis", "phalloplasty" "fertility function". We excluded pediatric patients with aphallia or adult patients with aphallia that re-assignments to be female. Only five of the case reports were adult patients with aphallia that reported their fertility function and remains the gonadal existence. All samples have fertility potential disregard their aphallia based on primary testicular function, semen analysis, hormonal profile radiological investigation. Radiology supporting to the investigation of fertility function has aimed to detect genitourinary anomaly related to the site of urinary meatus associated with death rate. Four patients showed post sphincteric meatus urinary and one patient was presphincteric meatus urinary. Gonadal existence is addressed in the case report. This report suggested that sex assignment on aphallia patients should be considered based on the gonadal existence because even though they do not have a penis, they can have children through assisted reproductive technology provided that their phenotype and genotype are matched.

Keywords: Absence Penis, Fertility Function, Gonadal Existence, Penile Agenesis, Phalloplasty, Sex Reassignment, Reproductive Health Care

Introduction

Aphallia was first described by Imminger in 1853 (Haller *et al.*, 1957). This case is a very rare congenital disorder. The prevalence of aphallia is 1 in 10-30 million live births (Bothra and Jain, 2012). As well Skoog and Belman reported that until 1989 there were only 60 cases of aphallia (Skoog and Belman, 1989). It is estimated that less than 100 cases have been reported to date (Joshi *et al.*, 2015). Aphallia is included in the non-hormonal differences or Disorders of Sex Development

(DSD) group (Gautier *et al.*, 1981). Aphallia in typical anatomical appearance, found no two corpora cavernosa and one corpora spongiosum, a developing scrotum a palpable testis in the scrotum (Gabler *et al.*, 2018). Because the penis was absent, micturition and coitus function will be disturbed (Raveenthiran, 2017). Interestingly, even though patients with aphallia do not have penises, they have normal sex hormones level and normal male karyotyping. A local abnormality of the genital tubercle can produce this condition. External genitalia will develop induced by Dihydrotestosterone

(DHT) (Evans *et al.*, 1999). Dihydrotestosterone, a testosterone derivative, will distinguish the remaining male external genitalia characteristics (Gautier *et al.*, 1981). The SRY gene encourages primitive sex cords to develop into Sertoli cells, which will generate fetal testes and Leydig cells in male fetuses with Y chromosomes. 5-reductase type 2 converts testosterone to dihydrotestosterone, which is produced by Leydig cells. Dihydrotestosterone binds to androgen receptors, which cause the genital tubercle to lengthen and expand (Sullivan and Rizaliyana, 2021)

There is a controversy over the definition of aphallia intervention among experts. Even though gender reassignment during childhood has historically been viewed as the best choice for these children (Demirer *et al.*, 2015), the expert's decision in choosing gender reconstruction must go through discussions with the patient and his/her family while still taking into account the socio-sexual future and the patient's fertility (Kumar and Faiz, 2015). In the past, urethral transposition and female sex assignments were performed for most of the aphallia. This female sex assignment is easier to do, with better results in terms of cosmetics (Bruch *et al.*, 1996) but in recent years, there has been a shift in the gender reconstruction of aphallia. The underlying of this change is a mismatch between genotype and phenotype. Because androgens play a role in the forming of gender and psychosexual identity, female sex assignment followed by hormonal therapy or psychosexual manipulation cannot change the formation of male gender identity and psychosexual (Reiner and Kropp, 2004; Reiner, 2004; 2005), so the current consensus is better for aphallia raised as a male and maintains the original phenotype (Oliveira *et al.*, 2016).

Some of the previous literature has focused on the surgical techniques and complications of urethral and penile reconstruction, the process of sex determination, genetics of aphallia and emergency conditions

associated with aphallia, or the long-term effects of sex assignment from aphallia from the psychosexual side (Bhandari *et al.*, 2011; De Castro *et al.*, 2007; Parisi *et al.*, 2007).

The fertility function of male aphallia gets very little attention compared to sexual function. The purpose of this study is to review the gonadal existence and supporting investigation related to the type of intervention from a case report of aphallia patients.

Materials and Methods

A narrative review was used as a method. It was obtained from searching Pubmed and Google Scholar, with the keywords "absence penis", "penile agenesis", "phalloplasty" and "Fertility Function". We selected the most relevant articles for this study. The literature must be in case report types of adult aphallia and reported their fertility functions such as karyotyping, physical examination, semen analysis, hormone reproduction level, sperm retrieval, radiological investigation type of intervention. We excluded pediatric patients with aphallia or adults with aphallia but assigned them to females. We only found seven case reports of the patient with aphallia more than six years old. Only five case reports were included in this review. Two case reports reported about patients with aphallia that underwent female sex reassignment.

Results

From the results of the literature search, between 1961 and 2021, we found only five published articles about adulthood aphallia that explored the fertility function and testicles preserved as male sex assignment. The number of studies that include the fertility potential of an adult male with aphallia in detail is inadequate. Five articles that are suitable for this topic, we summarized in Table 1.

Table 1: Profiles of adult patients with aphallia whose gonadal existence preserved related to fertility function

Author, year and type of report	Patient's description	Phenotype	Genotype /other genetic mutation	Follow up fertility function and other comments	Radiology appearance	Type of intervention	Result
Attie (1961) Case report	A 22-year-old male	Palpable testis in normal scrotum. Ductus deference and epididymis were palpable with normal size and consistency. A post-sphincteric urethral Rectal examination: A normal prostate and seminal vesicles were palpated.	46, XY	Normal sperm concentration (20- 90 million per cubic centimeter of semen analysis repeated) Morphological abnormality % PR 65% motile 3 h 0 after emission at room temperature.	Excretory urography and cystoscopic examination: Complete agenesis of the left kidney and ureter cystoscopy: The misplaced urethra Bladder capacity was in normal lower limit: 250 to 300 cc (normal capacity bladder in an adult is approximately 300-400 cc) -Normal bladder walls.	Urethral reconstruction phalloplasty	Not mentioned
Chibber <i>et al.</i> , (2005) Case report	A 16-year old male	Bilateral palpable testis in the normal scrotum A post-sphincteric urethral	46, XY	Asymptomatic at one year follow-up. The anal opening was normally	Bilaterally normal kidneys by ultrasonography and IVP was normally located	Urethral reconstruction	The patient would be potentially be fertile
Wang <i>et al.</i> (2011) Case report	A 30-year old male	palpable testis in the normal scrotum The anal opening	46, XY There was no AZF	Testosterone, prolactin, estradiol, LH/FSH hormone profiles were normal	USG: A thick-walled bladder was present.	Epididymectomy and right	Possible have a child by ICSI

Tabel 1: Continue

		was normally located A post-sphincteric urethra meatus	and SRY deletion	Progressive sperm on wet preparations that sperm retrieved by TESE	IVP: A left solitary kidney without hydronephrosis or ureteric dilatation Voiding cystography: There was an oval-shaped urethra was observed between the apex of the coccygeal and the bladder in the lateral position MRI: A complete agenesis penis, testis normal in the scrotum, urethra running from posterior to the apex of prostate and corpus spongiosum of the penis in sagittal and coronal T2-weighted images. MRI: A complete absence of the penis, a fistulous tract between the posterior wall of the bladder and the anterior wall of the rectum	nephrectomy because of congenital dysplasia at 28 years old	
Ekka <i>et al.</i> (2015) case report	A 32-year old male	Scrotum is normal. The presence of rugosity and hairs in the dark skin of the scrotum. The testes are palpable in the scrotum. A median raphe is present at the midline.	46, XY Secondary sexual characters were well developed. A presphincteric urethral meatus	Serum testosterone and FSH levels were normal		Suprapubic cystostomy urethral dilator passed through the vesico-rectal tract	Not mentioned
Pal and Pal (2020) Case Report	A 45-year old male	Testes are palpable in the scrotum. Size, shape and consistency are consistency are normal. Rugosity was present on the scrotum. Pubic hairs are present with normal male pattern distribution. Post spincheric meatus urinary.	Not mentioned	There were no dysmorphic features or clinical evidence of any other associated anomaly.	Ultrasound: Agenesis of the right kidney and ureter, the other organs in pelvic and abdominal are normal. Meatal stenosis and distal urethral stenosis	Meatal dilatation and cystoscopy	Not mentioned

LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; TESE: Testicular Sperm Extraction; ICSI: Intracytoplasmic Sperm Injection; AZF: Azoospermia Factor; PR: Progressive Spermatozoa; SRY: Sex-Determining Region Y Gene; USG: Ultrasonography; IVP: Intravenous Pyelogram; MRI: Magnetic Resonance Imaging

Discussion

We found that the highest age range in the adult patient with aphallia was 45 years the lowest was 16 years. According to Skoog and Belman (1989), the survival rate among aphallia patients is high reported at 87% in the post-sphincteric group, while the aphallia group with urethral atresia did not survive; the survival rate was 0%. The incidence of congenital anomalies was the most experienced in the aphallia group with urethral atresia. The most common causes of death were cardiopulmonary anomalies 11% or genitourinary anomalies 52% (Skoog and Belman, 1989; Aköz *et al.*, 1998; Stolar *et al.*, 1987). In this review, all patients have a high survival rate without any serious anomaly. Penile agenesis that is coupled with other malformations is substantially more common (54%) than isolated agenesis (Chakraborty and Chakraborty, 2018).

Primary sexual characteristics developed in aphallia patients, except penis. All patients in this review showed that bilateral scrotum was normal and testes were palpable in the scrotum (Attie, 1961; Chibber *et al.*, 2005; Wang *et al.*, 2011; Pal and Pal, 2020). Mirshemirani *et al.* (2009) reported the unilateral cryptorchidism in aphallia, but several testicles that do not descend into the scrotum are experienced by several aphallia (Mirshemirani *et al.*, 2009; Oesch *et al.*, 1987). About the ejaculatory duct and the accessory glands, only one patient was described as ductus deferens, The epididymis, vesicles seminal prostate. Glandula was palpable and normal by rectal toucher. This study is consistent with Carter *et al.* (1968) that reported that palpable epididymides and ductus deferens are in aphallia. Shamsa *et al.* (2008) also reported

that the ductus deferens of aphallia patients felt normal (Carter *et al.*, 1968; Shamsa *et al.*, 2008). The presence of the epididymis, vesicular seminal ductus deferens also indicates the development of the wolffian duct and AMH (Hannema and Hughes, 2007). From this data, it is suggested that aphallia is still able to produce seminal fluid through interactions between the testes (which contain germ cells, Sertoli cells Leydig cells), epididymis and male accessory glands (prostate, vesicle seminal and bulbourethral glands) that simultaneously contribute to this production process. The composition of the seminal fluid consists of 2-5% spermatozoa and secretory activity of the glands. Even though aphallia (patient 3) had an epididymectomy on the right epididymis but still had a functional left epididymis. The main function of the epididymis, beginning from transportation concentration to the maturation of spermatozoa, plays a role in determining male fertility. Post testicular defects display a normal morphological profile of spermatozoa sub-optimal capacitation, so the pregnancy was not happening (Sullivan, 2004; Hamada *et al.*, 2011).

Another important phenotype is the urethral opening. In this review, four patients were included in the post sphincteric (patient 1, 2, 3, 5) and one patient (patient 4) pre sphincteric category as classified by Skoog and Belman (1989) The anus is open and normal. Previous literature reported that there was not a single aphallia with absent urethral meatus and imperforate anus could be survived (Fahmy, 2016).

The experts agree that karyotyping should be performed on aphallia, even newborns, karyotyping being the first-line testing to detect specific X and Y (Lee and Coughlin, 2001). Almost all aphallia have 46, XY

karyotyping which confirms aphallia is genetically male. (Evans *et al.*, 1999). However, Soderdahl *et al.* (1972) analyzed the chromosome of the aphallia peripheral leukocyte tissue, which contained 1 cell 46, XXY (Soderdahl *et al.*, 1972). Other chromosomal results are normal. Unfortunately, karyotyping alone does not answer why aphallia can occur. Two pieces of literature examine a more specific candidate gene. However, Qiang *et al.* (2019) found chromosome 9 heterochromatin (9qh+) was responsible for the protective function and regulation of hereditary diseases and susceptibility to congenital disease from the father of aphallia's patients (Qiang *et al.*, 2019). Consistently Luo study showed that congenital aphallia is associated with congenital urethrectal fistula which is regulated by the same chromosome (Luo *et al.*, 2022)

Another examination to identify male fertility is whether there is a deletion or not on the Y chromosome that causes significant failure of spermatogenesis. The gene responsible for human spermatogenesis is the AZF locus. Azoospermia and/or oligozoospermia occur due to the deletion of this gene (Ozdemir *et al.*, 2007). In aphallia, SRY and AZF did not experience deletions, so they did not interfere with spermatogenesis.

In almost aphallia patients, the presence of testicles means that testosterone values are normal, proven by the response to the HCG test (Oesch *et al.*, 1987). This is consistent with several case reports, including four patients in this review, but one patient did not mention the hormonal investigation. One study assessed the testicular function by performing the HCG challenge test on the two aphallia patients. These patients showed significant increases in testosterone values (Gautier *et al.*, 1981). The HCG challenge test is necessary because it shows the presence of a functional testicle. Other studies about profile hormones found that testosterone, LH/FS, AMH, 17 hydroxyprogesterone, 4 androstenedione, inhibin B, Dihydrotestosterone (DHT), 5 α -reductase androgen receptors within normal limits in aphallia (El-Qadiry *et al.*, 2020; Bahe *et al.*, 2016; Coquet-Reinier *et al.*, 2007). The presence of all these hormones is like a fertile man, due to the presence of normal testicles like two patients in this review have a normal level of testosterone, prolactin, estradiol, LH FSH. Testosterone, LH, FSH are responsible for the development of sexual organs' maturity, secondary sex and spermatogenesis sperm maturation (Ismael *et al.*, 2017). Inhibin B and anti-mullerian hormone show normal Sertoli Cell function at prenatal, with at least one testis present. DHT is checked to calculate the DHT ratio. It is called a 5 α -reductase deficiency if the T/DHT ratio is >20:1 (Moshiri *et al.*,

2012). Another important hormone examination is the 5 α -reductase to find out if there is the 5 α -reductase deficiency that converts testosterone to DHT. The development of the internal genitalia depends on testosterone, while the external genitalia depend on DHT. Androgen receptors were examined to rule out Androgen Insensitivity Syndrome (AIS) (Mendoza and Motos, 2013)

Embryologically, sex development goes through two stages, namely sex determination and sex differentiation. The determination stage is when the fetus is still in a bipotential gonadal condition and the differentiation stage, occurs under the influence of factors produced by gonads (Sekido and Lovell-Badge, 2009; Fahmy, 2016). Sexual differentiation begins during the third month of intrauterine life when the external genitalia is established in the ectodermal cloacal fossa (Fig. 1). A swelling develops at an early stage. The cloacal fossa's anterior extremity is located in the midline, after that, a second swelling appears, the cloacal tubercle. The genital prominence is formed by the phallus and the-phallus. Cranially The cloacal tubercle generates a crescentic bulge on the phallus. The genital tubercle gives birth to the right and left genital tubercles. Swellings or folds are common. The enlarging of the penis is the phallus. It brings the phallic section of the urogenital sinus with it as it expands; In 21-26 mm embryos, a groove separates the glans from the rest of the body. The breakdown of the urethral wall creates the rudimentary slit-like urogenital opening. The phallic part of the urogenital membrane in embryos is broken down 12 mm in diameter (modified from McCrea, 2013). The clinical appearance of aphallia is complete testicle and sex secondary without a phallus (Fig. 2).

The cornerstone of male fertility evaluation is semen analysis according to WHO guidelines. Only two patients have performed semen analysis in an adult patient with aphallia. Semen analysis showed that normal sperm concentration and motile sperm morphology were even collected by TESE (Attie, 1961; Wang *et al.*, 2011). In a patient with aphallia, because of the absence of a penis and urethral opening in the anus, so sperm flow through the anus. If aphallia is analogous to an obstructive post testicular azoospermia, it is suggested that the spermatogenesis in the testes is normal. All men with obstructive azoospermia have sperm and making it possible to have biological children (Shin and Turek, 2013). Sperm retrieval and ICSI provides a bypass of post-testicular sperm damage during the transit of sperm in the genital tract (Esteves and Roque, 2019).

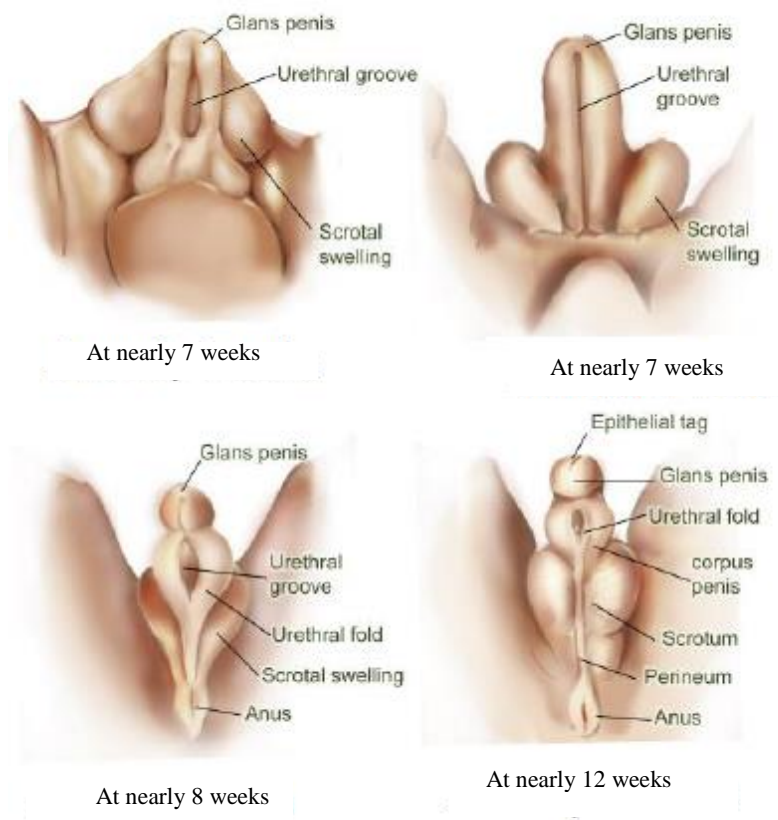


Fig. 1: Stage in development of the external genitalia of the male (Modified from McCrea, 2013)

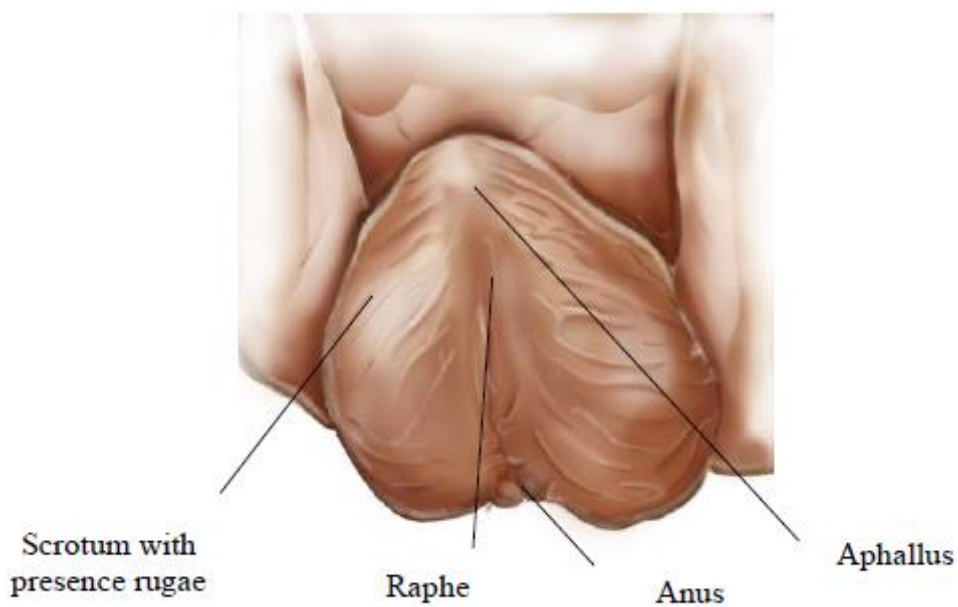


Fig. 2: Schematic male external genitalia. There are testicles in the scrotum, median raphe, presence of rugae anal

Radiological examination is used to confirm the structure of the embryo with the same origin at the time the gonads were formed, i.e., the urinary organs and the reproductive system are formed from the same origin: Mesenchyme (Chibber *et al.*, 2005). The radiological modalities were used ultrasound, IVP, cystography MRI. Ultrasound is used to identify the presence or absence of Mullerian and gonadal structures, especially the ovaries and uterus (Wright *et al.*, 1995). IVP examination assesses the urinary system abnormalities including kidney and ureteral tumors, urolithiasis other causes of low back pain, hematuria hydronephrosis. IVP assesses these urinary system abnormalities including kidney and ureteral tumors, urolithiasis other causes of low back pain, hematuria hydronephrosis (Hale *et al.*, 2014). Cystography was used to determine urethral anatomy, bladder outflow obstruction, vesicoureteric reflux the relationship between the genitourinary and gastrointestinal systems. MRI and cystography are complementary in the evaluation of aphallia (Goenka *et al.*, 2008). The images obtained from MRI are more representative than the other imaging (Wang *et al.*, 2011). In this review, from the overall radiological modalities for aphallic patients, it can be concluded that the urinary bladder, testes scrotum are normal. The organs which are often found abnormal in aphallia are the penis, kidneys urethra: A complete absence of penile, absence of the left kidney and ureter, urethra were misplaced, ureteric dilatation, a fistulous tract between the posterior wall of the bladder and the anterior wall of the rectum, oval-shaped urethra was observed between the apex of coccygeal and the urinary bladder in the lateral position (Chibber *et al.*, 2005; Wang *et al.*, 2011; Pal and Pal, 2020).

One of the treatment options for aphallia is surgery. The goals of aphallia surgery are to make the external genitalia ambiguous to be gender compatible, prevent urinary obstruction or infection, maintain sexual potential and fertility and maximize existing anatomical features to improve sexual function (Hoebeke *et al.*, 2015). Ciftci *et al.* (1995) in their case report and literature review concluded that up to 1995, only 18 cases of aphallia were raised in men. Reiner (2004) conducted a longitudinal study of 18 patients with DSD 46, XY who were diagnosed with cloacal and classic exstrophy, partial androgen resistance, mixed gonadal dysgenesis aphallia. Fifteen of these 18 patients underwent a female sex assignment who remained alive according to the results of the operation, 6 people (35%), while those who lived as men even though they had surgery to become women had a greater percentage of 10 people (59%) and 1 of 18 patients (6%) abstained, this patient who refused to mention his sexual orientation: Male or female, had a history of suicide attempts and recurrent murder ideas (Reiner and Kropp, 2004). In this

study, it was also reported that 3 of 18 patients were conducted male sex assignments. Male sex assignment is a better outcome because they had no gender-related problems and had a normal sexual orientation. Gonadectomy in a patient with DSD causes significant distress and exacerbates depression (Schützmann *et al.*, 2009). Meyer-Bahlburg (2005) reported that up to 2005, 16 Only two patients have performed semen analysis. Semen analysis from one patient (patient 1) found normal sperm concentration, morphology motile sperm similar to sperm motility results found in patient 3, even collected by TESE (Attie, 1961; Wang *et al.*, 2011). It is suggested that the spermatogenesis in the testes is normal. In aphallia, the absent penis and urethral opening in the anus, so that sperm flow through the anus. If aphallia is analogous to an obstructive post testicular azoospermia, then all men with obstructive azoospermia have sperm and making it possible to have biological children (Shin and Turek, 2013). Sperm retrieval and ICSI provides a bypass of post-testicular sperm damage during the transit of sperm in the genital tract (Esteves and Roque, 2019). Three patients (patients 1, 4, 5) were quantitatively fertile, but they were not performed with other specific investigations related to their fertility (Chibber *et al.*, 2005; Pal and Pal, 2020).

This review only contains five case reports that discussed gonadal existence and are preserved. Apart from the very rare and selected population of aphallia patients in early infant life, feminizing genitoplasty makes aphallia patients do not undergo specific tests regarding their fertility. Socioeconomic factors also limit the exploration of fertility in these patients. There is some literature on aphallia that includes potential fertility, but in these patients, a feminizing genitoplasty is performed because of the high difficulty of making a penis with a burden on the family. The other reason was the loss of follow-up patients in the middle of completing the preparation for surgical intervention or even refusing at all at the first visit had often happened or the patient only comes when there are complaints related to the gastrointestinal and urinary tract. Fertility function in patients with aphallia received less attention from researchers than socio-sexual function.

Conclusion

Aphallia is a male without a penis for sperm transport and ejaculation. Male fertility is the result of the interaction of various organs in the urogenital system that carries out their function. The gonads, accessory glands, chromosomal, hormone profile, semen characteristic, AZF factor, SRY imaging of aphallia patients are parameters for knowing fertility function.

The male sex assignment is a rational choice for aphallia. This report suggested that sex assignment on aphallia patients should be considered based on the gonadal existence. They only do not have a penis but can

have children through assisted reproductive technology provided their phenotype and genotype are matched. As a suggestion, if one day pursues a case of aphallia, then it is necessary to investigate the candidate gene that plays a role in this aphallia in addition to routine examinations supporting cases of disorder or different sex development.

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Author's Contributions

Eni Maria Sisca: Collected the data and contributed to the writing of the manuscript.

Cennikon Pakpahan: Designed the paper and conducted interpretation of the Data.

Andri Rezano: Conducted interpretation of the results and discussion.

Ria Margiana: Prepared Picture of the schematic male external genitalia and stage in the development of male external genitalia. Conducted interpretation of the Data.

Agustinus Agustinus, Tjahjo Djojo Tanojo: Conducted interpretation of the results.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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