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Cosmetic Outcome of Feminizing Genitoplasty in DSD (Disorders of Sex Development)

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Abstract:

Feminizing genitoplasty is an operation that may modify the genitals for correcting any birth abnormalities or to modify the genitals in sexual reassignment procedures. Feminizing genitoplasty might need a series of operations. The findings of childhood operations for women have been published by international clinics and Disorders of sexual development teams. However, studies focusing on short-term results may not accurately reflect longer-term results. Genetic testing is crucial for evaluating patients with DSD, as it helps predict phenotype, clarify recurrence risk, and aid in making medical decisions. Peripheral blood karyotype analyses detect X & Y chromosomes, while fluorescence in situ hybridization (FISH) helps assess sex chromosome mosaicism and Yp rearrangements. Scientists repair the phallus within cases with ambiguity and significant clitoral hypertrophy before vaginoplasty. The incision is marked using a skin scribe, retracted, and parallel lines drawn.

Keywords: Cosmetic outcome, Feminizing Genitoplasty, DSD

1. Introduction

Disorders of sexual development (DSD) are a number of congenital disorders that are related to the atypical development of internal and external genital structures. These disorders may be related to variances in genes, hormones, & developmental programming. Due to the ambiguity of the external genitalia, impacted individuals might be identified at birth. Others might have postnatal virilization, delayed/absent puberty, or infertility at a later time. The documented prevalence of genital ambiguity has been determined to be between 1:2000 and 1:4500 **(1)**. Sexual development is accomplished through the accurate synergistic temporal-spatial expression of a variety of repressing & activating factors. Disorders of sex development may arise as a

consequence of changes in this recognized developmental sequence. The molecular basis of DSD cases has been clarified through the examination of numerous genes and genetic regulatory mechanisms included in this process. Gene expression is influenced by tissue specificity, programming, and relative doses to determine the fate of cells **(2)**.

The aim of this study was evaluation of cosmetic outcome of feminizing genitoplasty in DSD.

Disorders of sexual development (DSD)

The incidence of XY women is 6.4 per 100,000 live-born women, regarding the Danish Cytogenetic Central Registry. The median age at diagnosis was 7.5 years, and the incidence of androgen insensitivity was 4.1 per 100,000 live births in this study. The median age at diagnosis was 17 years, and the incidence of XY gonadal dysgenesis was 1.5 per 100,000 live-born women. The southern African population has the greatest incidence of DSD, with the incidence varying within ethnic groups **(3)**.

EMBRYOLOGY

The reproductive tracts' sexually dimorphic development is affected by a variety of factors. The typical development of sex is based on an accurate spatiotemporal pattern of repressing & activating factors interacting in a synergistic orchestration **(4)**. The sex chromosomes are responsible for determining sex. The binary switch that begins the male developmental program is the Sex Determined Region on the Y chromosome (SRY) gene, which is situated on the short arm of the Y chromosome. The testosterone importance for male sexual differentiation was demonstrated by the pivotal experiments conducted by Dr. Alfred Jost **(5)**.

GENETICS OF SEX DIFFERENTIATION AND DEVELOPMENT

Sexual development is accomplished through the accurate synergistic temporal-spatial expression of a variety of repressing & activating factors. DSD may arise as a consequence of changes in this recognized developmental sequence. The molecular basis of DSD cases has been clarified through the examination of numerous genes and genetic regulatory mechanisms included in this process. Gene expression is influenced by tissue specificity, programming, and relative doses to determine the fate of cells **(2).**

The initial differentiation of the bipotential gonad is influenced by the following genes: empty spiracles homeobox2 (EMX2), Wilms' tumor 1 (WT1), Chromebox homolog2 (CBX2), LIM homeobox factor 9 (LHX9), steroidogenic factor 1 (NR5A1), sine oculis-related homeobox 1/4 (SIX 1/4), and GATA binding protein 4 (GATA4) **(6)**. Consequently, the differentiation of the bipotential genital ridge to a male or female phenotype is influenced by cellular fate decisions. In this process, a complex regulatory network is involved, where the activation of one pathway, including the testicular pathway, results in the repression of the other pathway, the ovarian pathway, and vice versa **(7)**.

The ovary's differentiation is an active process that is based on the activity of specific factors, instead of being the "default pathway." In the pre-granulosa cell of the developing ovary, WNT4 inhibits the expression of SOX9. The expression of β-catenin is stabilized by WNT4 and RSPO1. FOXL2 is an additional nuclear protein and transcription factor that is essential for maintaining and differentiating the ovary. β-catenin accumulating in the nucleus is facilitated by the proteins WNT4 and RSPO1, which interact with LEF1 to stimulate the transcription of other genes. Additionally, the expression of SOX9 is suppressed by FOXL2 and β-catenin **(8)**.

CLASSIFICATION OF DSD

XX, DSD: 21-hydroxylase deficit, a frequent form of virilizing congenital adrenal hyperplasia, affects infant girls due to genital ambiguity. The condition can cause extensive external genitalia virilization, causing them to appear males with bilateral undescended testes **(9)**. Congenital adrenal

hyperplasia in infant boys usually appears at two to three weeks of age with symptoms like dehydration, failure to thrive, poor feeding, lethargy, hyperkalemia, hyponatremia, hypotension, & normal male sexual development. Delaying diagnosis can be lethal. The morbidity & mortality related to adrenal inadequacy may be reduced by newborn screening programs. Other steroidogenesis disorders may also be associated **(10)**. Mutations in ovarian factors genes cause premature ovarian failure & ovarian dysgenesis. In SERKAL syndrome, WNT4 mutations result in renal, adrenal, and lung dysgenesis, as well as the reversal of sex from female to male **(11)**.

XY, DSD: Cases having irregular testicular differentiation, deficiencies in the biosynthesis of testosterone, as well as diminished testosterone activity may have phenotypes including gonadal dysgenesis, campomelic dysplasia, congenital heart disease, Smith-Lemli-Opitz, WT1 syndromes, and other genes related to XY gonadal dysgenesis. These conditions can manifest in facial features and syndactyly of the 2^{nd} or 3^{rd} toes **(9)**. In XY persons, MAP3K1 mutations seem to alter signaling pathways in order to enhance ovarian differentiation and inhibit SOX9 **(12)**. Undervirilization is linked to mutations in proteins essential for biosynthesis of testosterone, including SF1, LHR, StAR, cholesterol desmolase, CYP11A1, CYP17A1, HSD3B2, HSD17B3, AKR1C2/4, POR, and SRD5A2 **(13)**, AR/NR3C4 mutations disrupt testosterone signaling, causing a range of phenotypes from normal female external genitalia to male infertility in adulthood **(14)**.

Sex chromosome DSD: Turner syndrome is a rare genetic condition defined as aneuploidy or structural X chromosomes rearrangements, affecting one within 2500 live-born women. It can be diagnosed during neonatal periods due to short neck, low birth weight, lymphedema, also, delayed puberty **(15)**. Around fifty percent of girls are born with congenital heart disease, and the highest risk is observed in girls having forty-five, X karyotypes. Growth hormone therapy enhances stature, whereas estrogen and progesterone hormone therapy stimulates the development of 2ry sexual features and prevents the risk of osteopenia **(16)**. Klinefelter syndrome, a rare genetic disorder affecting 1 in 500 males, can lead to abnormal external genital development, dyslexia, behavior difficulties, and autism spectrum disorders **(17)**.

XX, Sex Reversal, Ovotesticular Disorder, and XY, Sex Reversal Disorder

Ovotesticular disorder is a medical condition where a case has both seminiferous tubules & ovarian follicles, influenced by gene expression patterns and hormone secretion function. It can be caused by testis activation otherwise insufficient expression of genes that are pro-ovary or anti-testis **(18)**. The DAX1 gene, located in the Xp21.2 region of the X chromosome, is linked to XY sex reversal, congenital adrenal hypoplasia, & XX sex reversal, highlighting its genetic complexity **(19)**.

Persistent Mùllerian Duct Syndrome (PMDS)

PMDS is an uncommon autosomal recessive condition affecting males, causing Mùllerian structures persistence. Usually diagnosed during inguinal hernia or cryptorchidism surgery, it often results from abnormal male excretory duct development and fertility. **(20)**.

Urogenital anomalies

Uterine malformations, such as cloacal and bladder exstrophy, are common in patients with DSDs and can range from 5.5-9.8%. These malformations may be related to renal cysts, HNF1B mutations, MODY 5 diabetes, mutations of HOX gene, GATA3, FRAS1, FREM, WNT genes, & syndromic ciliopathies **(21)**.

GENETIC TESTING IN DSD

Genetic testing is crucial for evaluating patients with DSD, as it helps predict phenotype, clarify recurrence risk, and aid in making medical decisions. Peripheral blood karyotype analyses detect X & Y chromosomes, while FISH helps assess sex chromosome mosaicism and Yp rearrangements. **(22)**. Chromosomal microarray analyses, like SNP microarrays otherwise array

CGH, have the potential to identify novel candidate genes related to DSD by detecting submicroscopic gene alterations. Customized CGH can accelerate diagnostics and reduce costs. Genome-wide association studies (GWAS) provide a hypothesis-free method in identifying novel loci related to DSD; however, their utility is limited by the low prevalence of particular conditions and the phenotypic and genetic variation **(23)**. Genomic changes near SOX9 can modify chromatin structure and alter gene regulatory relationships. Non-coding changes near SOX9 are related to phenotypes like campomelic dwarfism and XX female to male sexual reverse. Long-range regulatory elements can disrupt gene expression. AIS, reduced protein levels, and aberrant splicing may be the result of AR mutations that are placed outside the coding region **(24)**.

GENETIC TESTING ETHICS

WGS and WES are crucial for identifying diseases' molecular basis, however, they can also identify genetic changes that are not associated with sexual differentiation. Informed consent and counseling are needed, and NGS has limitations like inability to characterize variant significance **(25)**.

GONADAL TUMORS

Gonadectomy decisions require individualized care with multidisciplinary involvement and molecular understanding. The accessibility of physical examinations, the possibility for fertility, and the risk of malignant degeneration are all critical factors. Dysgenetic gonads with a Y chromosome are at high risk for neoplastic transformation **(26)**. Testes removal within cases having complete androgen insensitivity is controversial, but the risk of cancer development is few until early adult years. Many women with CAIS opt for laparoscopic gonadopexy, gonadal biopsy, molecular screening, and ultrasound surveillance to avoid gonadectomy, promoting shared decision-making **(27)**.

SURGERY IN DSD

Individuals with DSD require individual considerations for operation, including future fertility, risk of tumors, urinary tract infections, avoiding stigma, & ensuring functional genital anatomy for penetrative intercourse **(28)**. Early operations on the genitals were found to result in a favorable result for girls with CAH. The available result reports consist mainly of small clinical series that exhibit diagnostic heterogeneity. Crucially, there is even less available data on the results of untreated DSD **(29)**.

FERTILITY POTENTIAL AND PRESERVATION

The preservation of fertility through oocyte, embryo, or sperm banking is currently being investigated for people with chronic illnesses like tumors. Preterm kids who have tumors are currently undergoing the development of experimental strategies. Finlayson and his colleagues suggest a paradigm shift **(30)**. The report suggests optimism about assisted reproductive technologies, citing a live birth and successful intracytoplasmic sperm injection procedure within a female having uterine agenesis, & the need for multidisciplinary care. **(31)**.

Feminizing genitoplasty and its outcome

Feminizing genitoplasty is an operation that may modify the genitals for correcting any birth abnormalities or to modify the genitals in sexual reassignment operations. A series of operations might be necessary for feminizing genitoplasty **(32).**

Vaginoplasty, Clitoroplasty, and labiaplasty are the most frequently performed forms of feminizing genitoplasty **(33)**.

Vaginal surgery is used to allow unobstructed menstrual flow in individuals with CAH or develop a vagina that is appropriate for intercourse for persons with vaginal hypoplasia. Vaginal dilator technique is the initial therapy for vaginal hypoplasia, and it’s efficient in up to eighty-five percent

of females. Effective vaginal development depends on compliance and emotional maturity, with psychological input being essential for assessing readiness for dilation. **(34)**. An examination under anaesthetic is recommended for uterine presence, usually performed around age 10. Postoperative dilation may be recommended for patency, but emotional maturity is needed. Vaginal operation must be carried out during adolescence, as the hypo-estrogenized vagina of prepubertal age could be tender and painful. Endogenous oestrogenisation might promote healing **(35).** Feminising procedures aim to improve sexual function for individuals with DSD, but long-term data is limited. Sexual function issues are more prevalent in people that are impacted, with vaginal hypoplasia being more common. Recent studies show surgical vaginoplasty patients experience more issues **(36)**.

The study compares DSD patients with clitoral operation & those without demonstrated insignificant rise in decreased sensation & anorgasmia. Using validated sexual function measures, caution is needed as some require partner participation, potentially masking difficulties **(37)**.

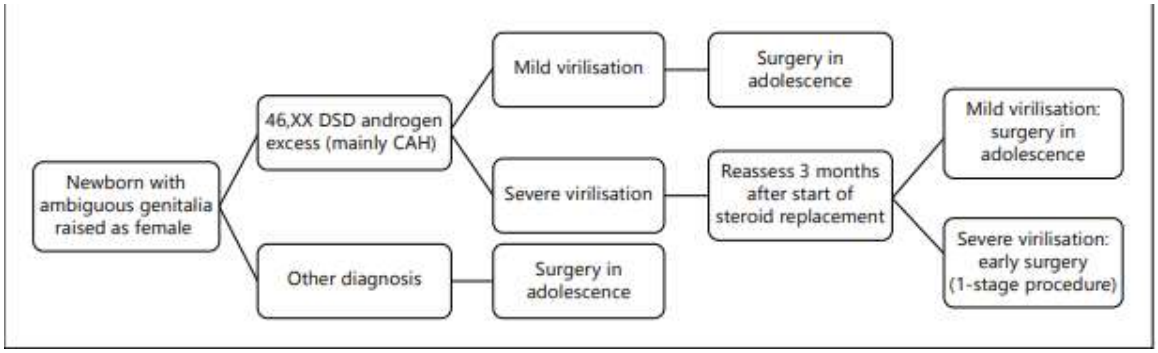

Figure (1): Provisional guideline of feminising surgery (38).

Suggested Treatment Approach

The evaluation in feminizing operation must be delayed for three months following the completion of proper replacement therapy. This will enable the parents to adjust to their daughter's diagnosis and recover physically. The decision to provide early operation is based on the extent of genital masculinity that remains following suppression therapy, which is influenced by labial fusion and confluence due to embryonic androgenisation **(39)**. Early surgery requires consensus within a multidisciplinary team, considering pros and cons, and presented to parents for informed decision-making. Parents' ability to cope with aberrant genitalia should also be considered **(40)**. Reconstruction of female patients mainly involves 2 groups: cases having extreme androgen stimulation, mixed gonadal dysgenesis, or true hermaphrodites, and girls who are born with pure urogenital sinus irregularities. Successful reconstruction relies on accurate preoperative anatomy, including urogenital sinus abnormalities. Primary assessment involves a history, physical investigation, and labial anatomy **(41)**. Severe UG sinus cases often cause anterior rectum displacement, affecting cloaca. A pelvic & abdominal ultrasound examination is crucial for identifying uterus, vagina, and gonads, with UG sinus anatomy being a key consideration **(42)**. Endoscopy is crucial for identifying UG sinus abnormalities, which can be classified into 4 forms: distal confluence, labial fusion, high, proximal confluence, & absent vagina. If genitography isn't available, a catheter may be left within the vagina **(43)**.

Vaginal reconstruction has evolved toward 4 basic procedures

The cut-back vaginoplasty must be utilized exclusively with simple labial fusion **(44).** The flap vaginoplasty involves the anterior detachment of the vagina, although the posterior wall of the UG sinus is also opened. Those sinuses with an infrasphincteric, low confluence were properly treated with the procedure **(45)**.

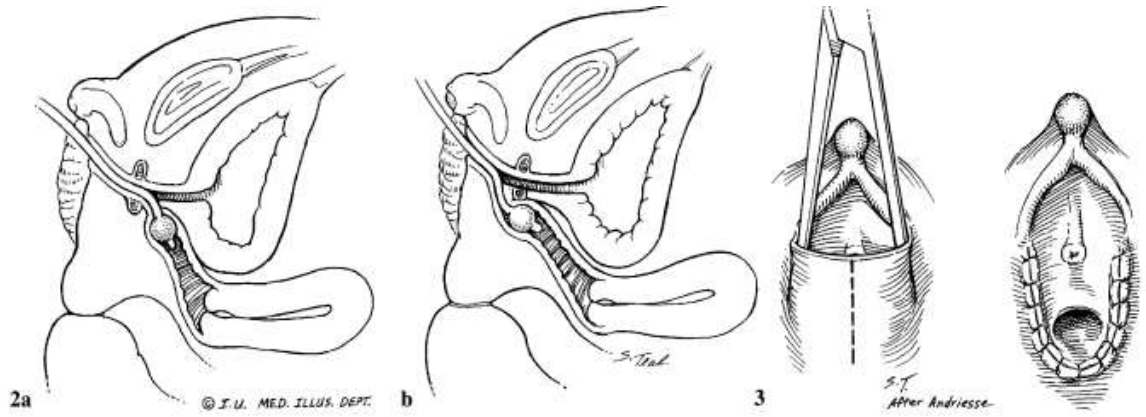

Figure (2): 2a, b Spectrum of vaginal confluence with the urethra. a High (suprasphincteric) confluence. b Low (infrasphincteric) confluence Figure. 3 Cut-back vaginoplasty **(46)**.

Operative techniques

Preoperatively, patients with vaginal confluence undergo enema and Golytely bowel preparation, antibiotics, endoscopy, Fogarty catheter, sponge, and povidoneiodine preparation. The cas is positioned through an aperture in drapes for simple entry, and the lower half of the child is disinfected with povidone-iodine. Clitoral hypertrophy is addressed first **(47)**.

Surgical treatment of the clitoris & low vaginal confluence

Scientists repair the phallus within cases with ambiguity & significant clitoral hypertrophy before vaginoplasty. The incision is marked using a skin scribe, retracted, and parallel lines drawn **(48)**. The procedure involves making incisions around the phallus, urethral meatus, and preputial skin, identifying the neurovascular bundle, and making lateral incisions. The cavernous erectile tissue has been dissected and removed, & the glans is suture-ligated to maintain its connection to Buck's fascia and ventral plate **(49)**.

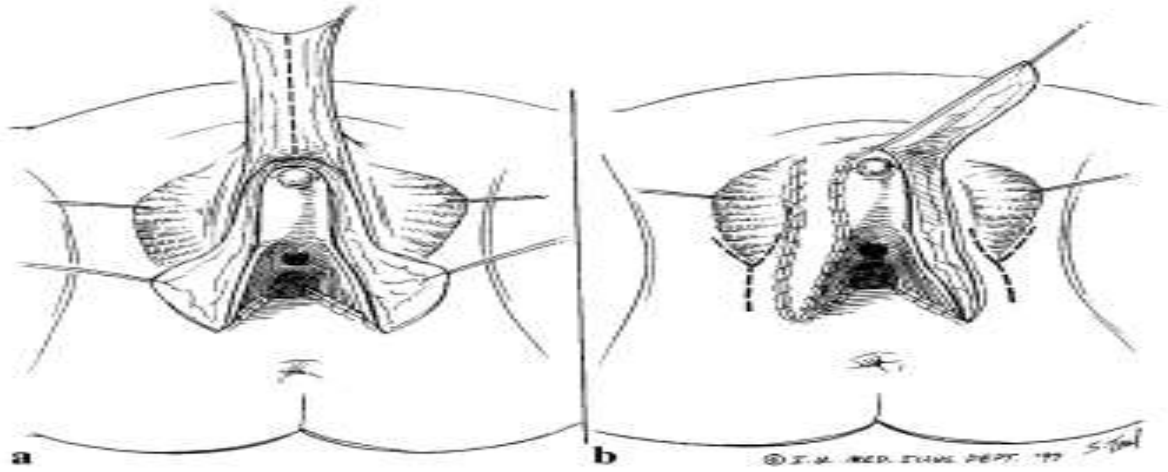

Figure (3): A: The UG sinus is extensively opened by the posterior flap being sewn in situ. Proposed incision into the phallus. b: the labia minora are formed by splitting the phallic skin in the midline. Incisions at the base of the labia majora to facilitate inferior placing alongside the vagina **(46)**.

Reconstruction of the high, or supersphincteric, vaginal confluence

Scientists agree that the treatment of high vaginal Takeo must include a full separation of the vagina from the UG sinus & the modification of a vaginal pull-through procedure. Separation can be challenging due to limited exposure, causing complications like strictures, fistulas, diverticulum formation, and vaginal stenosis. Delays in vaginal plasty are recommended due to these difficulties **(50)**. The rectum is retracted using a small Deavor retractor, exposing the entire UG sinus. The back wall of the vagina is dissected at an elevated level, and Donahoe recommends that it be extended to the peritoneal refection to facilitate mobilization. The Deavor retractor is positioned within the vagina, thereby enabling a greater degree of anterior wall exposure at a distance from the proximal urethra & bladder. Err on the side of entering the vagina instead of the urethra, as this method is more prone to providing clear vision for retubularization of the UG sinus as a neourethra **(44)**.

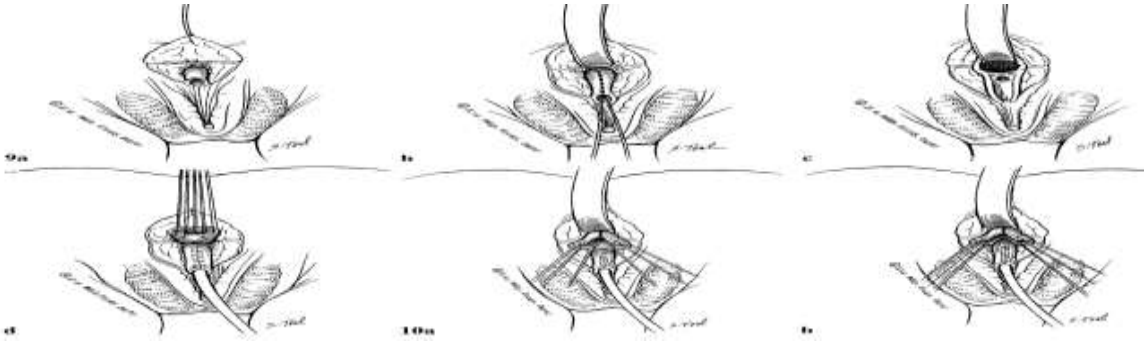

Figure (4): Approach that is posteriorly inclined. a The posterior ¯ap is elevated and dissection proceeds in the midline, exposing the UG sinus. b the intact rectum is elevated from the UG sinus using a Deavor retractor, and the proposed incision into the posterior wall of the UG sinus is observed. c the distal atretic vagina is used to access the UG sinus. The anterior wall of the retractor, which is currently located in the vagina, is exposed in conjunction with the urethra. The vagina is fully mobilized, and the UG sinus is closed in 2±3 layers, similar to the neourethra. (Reprinted with permission from Rink et al. **(51)**), 10a the posterior vaginal wall is exposed. b an opening is made in the anterior vaginal wall. (Reprinted with permission from Rink et al **(51).**

The procedure involves removing the vagina using an absorbable suture and a Foley catheter. Healthy fatty tissue may separate the urethra from the vagina. In sinus-located vaginas, the vagina can be mobilized to the perineum without an anterior flap. The vagina is usually atretic and should be opened anteriorly and posteriorly **(52)**.

A Foley catheter is placed in the vagina, and a Penrose drain is placed for 3 days. A perineal dressing is placed, and several flaps are developed. A transtrigonal approach is proposed for high vaginas, but only necessary in a few patients after unsuccessful attempts at detaching the vagina from the perineum **(53)**.

Timing of the procedure

The timing of vaginoplasty, especially for cases with high confluence, was a topic of debate. However, recent research suggests a posterior prone approach, which can be performed early in life, even within cases under 6 months old, and potentially use the phallic skin as an anterior flap **(44)**. Donohoe & Gustafson reported successful one-stage vaginal repair within kids of 8-12 months, finding no increased risk and no difficulty. DeJong and Boemers proposed earlier repair in the first 3-4 weeks of life, citing maternal and placental estrogens and vaginal wall hypertrophy for easier mobilization. Although not performed in the first month, early reconstructions offer significant surgical and psychological advantages **(54)**.

Postoperative care

Scientists use endoscopy for children with high vaginal takeo to evaluate urethral & vaginal reconstruction. The posterior prone approach was successful within 12 patients, with one having a small fistula **(55)**.

SURGICAL OUTCOMES

The findings of childhood operations for women were published by international clinics and disorders of sexual development teams. However, studies focusing on short-term results may not accurately reflect longer-term results. Caution should be taken when interpreting early outcomes, as objective measures of sexual functioning and life quality are crucial. Different surgical groups report disparate cosmetic outcomes, with dissatisfaction with cosmesis ranging from 30% to 100%. In a research, forty-six percent of girls having CAH reported unsatisfactory clitoral appearance due to atrophy or absence **(56)**. The Australian experience of cosmesis in childhood feminizing genitoplasty was favorable, with 72% having good genital appearance. Repeat surgical procedures are common at puberty, with 98% of adults requiring treatment, including major surgical revisions. The most common cause of more treatment is vaginal stenosis, which indicates a vagina not suitable for vaginal intercourse. Studies have reported that cosmesis occurs within eleven, thirty-six, & one hundred percent of researches evaluating findings of childhood feminizing genitoplasty **(57)**. In CAIS & Mullerian agenesis (MRKH syndrome), most patients desire a neovagina, preferring active vaginal dilatation over operational techniques like colonic interposition, split thickness skin grafting, & laparoscopic-related peritoneal vaginoplasty, due to potential complications **(58)**.

PSYCHOSEXUAL OUTCOMES/QUALITY OF LIFE MEASURES

Life Quality for females with DSD involves arousal, intimacy, self-esteem, sexual function, mental health, & social functioning. Studies show delayed sexual milestones, fewer partnerships, lower arousal, higher anxiety, lower self-esteem, & suicidal thoughts **(59)**. The study suggests that certain diagnoses, like mixed gonadal dysgenesis & CAH, may be more common in women with DSD. It suggests integrating psychosocial care from mental health staff into interprofessional care teams for better understanding and treatment **(60)**.

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