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UTEROVAGINAL AGENESIS: THE PREVALENCE, CLINICALS, AND QUALITY OF LIFE FEMALE WITH MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME IN INDONESIA

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Abstract

Preliminary: Primary amenorrhea, the absence of menstruation, is common among adolescent girls, with one of the causes being MRKH Syndrome. The psychological impact of MRKH can disrupt cognitive function and behaviour, posing challenges to individual adaptation. This study aims to understand the prevalence of MRKH syndrome, its clinical presentation, and the quality of life of affected individuals to enhance their well-being. **Method:** The study involved a cross-sectional observational design, which utilized medical records from 2004 to 2021 at Cebior Semarang. Furthermore, interviews were conducted with participants who agreed, employing a questionnaire based on the TAAQOL instrument. **Results:** Out of 218 patients diagnosed with primary amenorrhea and uterovaginal agenesis, 45.87% were between 12 and 43 years old. This condition is rare, comprising only 0.086% of recorded Disorders of Sex Development (DSD) cases. MRKH syndrome is predominantly categorized into Type I (98%) and Type II (2%). Clinical observations indicate some patients have absence labia minora, and have agenesis of the vagina and uterus. Hormone profiles were conducted for 25 of these patients. MRKH individuals continue to grapple with challenges regarding quality of life, particularly concerning sexuality. Correlation analysis demonstrates that higher cognitive abilities positively impact daily activities, while increased sexual activity adversely affects positive emotions. **Conclusion:** Challenges persist in enhancing the quality of life for females affected by MRKH syndrome, particularly in matters related to sexuality. Therefore, the involvement of healthcare professionals and genetic screening is crucial for improving their well-being.

Keywords: Genetic Aspects in Indonesia, MRKH Syndrome, Psychological Effects and Quality of Life.

INTRODUCTION

Various reproductive conditions can affect the health of women in the future, such as Primary Amenorrhea. PA a prevalent issue among teenage girls, is a leading disorder in gynecology. It is characterized by the absence of menstruation between the ages of 11 and 15, accompanied by variations in the development of secondary sexual characteristics. Research on its etiology, conducted extensively, suggests potential causes, including anatomical abnormalities of the reproductive tract, primary hypogonadism, hypothalamic dysfunction, pituitary abnormalities, multifactorial conditions or disorders of other endocrine glands like polycystic ovary syndrome (PCOS). However, obesity and insulin resistance are metabolic disorders found in women with PCOS. Common causes include gonadal dysgenesis and Mullerian

agenesis, while less common ones encompass hypogonadotropic hypogonadism, constitutional delay in puberty, and anovulation[1–3].

PA can be categorized based on the presence of the uterus, determined by ultrasound or MRI. Conditions or differences in sex development (DSD) may lead to the absence of the uterus in females with typical external genitalia. DSD conditions like Müllerian agenesis and complete androgen insensitivity syndrome (CAIS) are major contributors to PA. When secondary sexual characteristics are present, a uterine ultrasound is recommended. If the uterus is not detected, karyotype analysis is conducted. A primary amenorrhea case with a typical female karyotype (46, XX) but uterus absence indicates Müllerian agenesis, also known as MRKH Syndrome[4] (Fig-1).

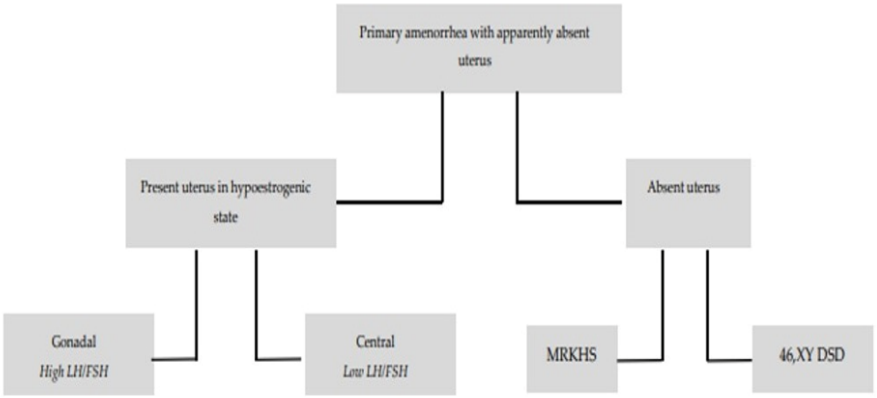

Figure 1: Considerations for Diagnosing Primary Amenorrhea[4]

Figure 1. Primary amenorrhea case with a typical female karyotype (46, XX)

Mayer-Rokitansky-Küster-Hauser syndrome, a common cause of primary amenorrhea resulting from gonadal dysgenesis, is characterized by normal karyotype, secondary sexual characteristics, and functioning ovaries in affected women. Despite this, they experience the congenital absence of the uterus and the upper two-thirds of the vagina. Occurring in about 1 in 5000 women, MRKH syndrome is deemed a rare disorder by the National Institutes of Health. It is classified into two types: Type 1, isolated, and Type II, involving multiple organs. The more severe manifestation of Type II syndrome is called MURCS. The exact cause of MRKH syndrome remains incompletely understood. While most cases are sporadic, indicating a non-genetic origin, certain genetic factors, such as mutations in WNT4 have been implicated in some instances[5].

Research on Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome is continuously evolving, covering various aspects from its etiology to genetic factors like GREB1L[6]. Studies investigating Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome have revealed regional variations in prevalence and characteristics. Research in China has shown a higher occurrence of Type II syndrome in Northern regions compared to Southern areas, although still slightly lower than in European cohorts. In Indonesia, gene mutations were identified in a notable proportion of patients studied. Furthermore, investigations have explored various treatment techniques, including neovagina creation and the Davydov procedure, while also evaluating sexual function and the influence of psychosocial support on patient well-being[7–11].

Individuals diagnosed with MRKH syndrome often experience a range of emotions such as shock, denial, melancholy, frustration, guilt, or resentment before accepting

their condition from physical, psychological, social, and emotional perspectives. Managing mental health concerns in these individuals aims to improve their overall well-being. One common method of assessing their well-being is through tools like the TAAQoL (TNO-AZL Adult Quality of Life), frequently used in Dutch medical studies to evaluate quality of life. This questionnaire addresses physical, psychological, and social challenges individuals may face in various aspects of their lives[12]. Genetic counselling is often necessary due to the psychological strain resulting from conditions like MRKH syndrome. It helps individuals and their families understand and adapt to the medical, psychological, and familial implications of genetic influences on disease. Therefore, this study aims to understand the prevalence of MRKH syndrome, its clinical features, and the quality of life of affected individuals, ultimately seeking to enhance their well-being[13].

RESEARCH METHODS

Study Design

The study adopts a descriptive observational approach with a cross-sectional design.

Population and Sample

Participants from 2004 to 2021 experiencing primary amenorrhea and uterine-vaginal agenesis, aged over 12 years[14] (aligned with the average age of menarche in the ASEAN region), were included. All individuals had a 46, XX karyotype and underwent comprehensive clinical assessments, including secondary sexual development indicators, external genital organ examinations, and ultrasound findings.

Methods

Data, including physical examination and chromosome information, were collected from medical records at the Molecular and Cytogenetics Unit, Faculty of Medicine Undip Semarang. Patients suspected of MRKH syndrome, who consented to participate, completed an Informed Consent form and assessed their quality of life using the TAAQOL questionnaire. This questionnaire evaluates health issues across seven scales, primarily utilizing questions with two parts: frequency of health problems experienced in the past month and emotional responses to these issues. A higher score indicates an improved quality of life regarding health[15].

Analysis of Data

The dataset's completeness was verified before coding, tabulation, and analysis using Jamovi statistical software version 2.4.1. Descriptive analysis was conducted to understand data characteristics, and correlation analysis explored relationships among seven psychological factors. Data distribution was assessed for normality, with the Pearson test used for normally distributed data and the Spearman test for non-normally distributed data.

Ethical Clearance

Ethical approval was granted by the Diponegoro University Health Research Ethics Committee (registration number 358/KEPK/FK-UNDIP/IX/2022).

RESULTS AND DISCUSSION

Prevalence and Clinical Aspects

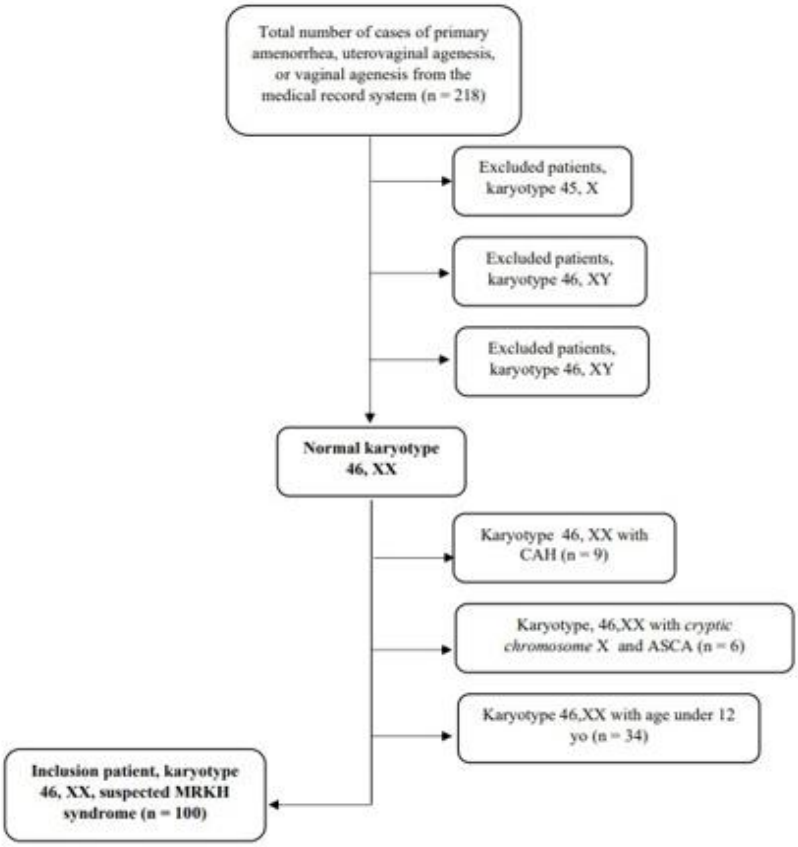

Figure 2: Research Flow Chart

The research flowchart shows that between 2004 and 2021, 218 patients underwent cytogenetic analysis at CEBIOR. Out of these, 100 patients (45.87%) met the inclusion criteria and were identified as suspected MRKH syndrome cases. In comparison to the total recorded DSD patients at CEBIOR in 2021, the suspected MRKH syndrome cases accounted for 0.0868%, which translates to 100 out of 1152 patients.

The patients, aged between 12 and 43 years old, most commonly presented at 18 years old. Among 100 patients suspected of MRKH syndrome, medical records classified 98 patients as MRKH Type I and 2 patients as MRKH Type II. MRKH Type II syndrome is characterized by additional abnormalities in the anorectal and renal areas.

Table 1. Sample Examination Result (n=100)

	Variable	Total
Labia	Absent	19
Minora	Present	81
Vaginal	No Introitus	12
	Have Introitus	88
Uterus	Atresia	5
	Agenesis	32
	Hypoplasia	63

Following clinical assessments by specialists, it was determined that 19 women exhibited labia minora agenesis, and 12 women presented with atresia of a vaginal introitus. Moreover, ultrasound and hormone examination findings were used as supportinng data. Ultrasound examinations revealed that 5 women had uterine atresia, 32 women had uterine agenesis, and 63 women had uterine hypoplasia (Table 1).

Hormonal examinations were conducted on 25 out of 100 patients who met the inclusion criteria. These assessments involved measuring FSH and LH levels, resulting in FSH levels of low 32%, normal 64%, and high 4%, and LH levels of low 44%, normal 36%, and high 20% (Table 2).

Table 2: Hormone Test Result (n=100)

Age (Years)	FSH (mIU/mL)			FSH (mIU/mL)		
	L	N	H	L	N	H
12 -22	7	7	1	7	4	3
23-33	1	9	0	4	3	4
34-44	0	0	0	0	0	0
*note : L (Low), N (Normal), H (High) Grouping by age						

Quality of Life in Female with Utero and Vaginal Agenesis

Seventy out of the 100 patients meeting the inclusion criteria completed the questionnaire voluntarily. The responses were subjected to quantitative analysis, including statistical and correlation data. The analysis revealed an uneven distribution of self-acceptance among suspected MRKH Syndrome patients.

Table 3: Statistical Data on Psychological Aspects

No	Psychological Aspects	Median (Min-Max)
1	Cognitive Function	14,1
		(7,5 – 16)
2	Sleep Problem	14,4
		(10 – 16)
3	Social Problem	12,5
		(10,5 – 16)
4	Daily Problem	13,3
		(11,5 – 16)
5	Sexual Problem	5,78
		(3 – 8)
6	Positive Emotions	19,8
		(13 – 24)
7	Negative Emotions	11,1
		(6 – 13)

Table 3 suggests that individuals suspected of MRKH Syndrome encounter ongoing difficulties in their quality of life, particularly in sexual issues. Correlation analysis was performed on psychological factors using the bivariate Spearman correlation test.

Derived from the rho findings, Table 4 illustrates notable correlations as outlined below:

Table 4: Correlation Analysis Between Psychological Aspects

Psychological Aspects	Correlation	Correlation Value	
		P	R
Cognitive Function	Sleep Problem	< 0.001	-0.406
	Social Problem	< 0.001	0.449
	Daily Activities Problem	< 0.001	0.998
	Positive Emotions	< 0.001	0.719
	Negative Emotions	< 0.001	0.635
Sleep Problem	Daily Activities Problem	< 0.001	0.612
	Negative Emotions	< 0.001	-0.479
Social Problem	Sexual Problem	0.016	-0.285
	Positive Emotions	< 0.001	0.696
Daily Activities Problem	Sexual Problem	< 0.001	0.673
	Negative Emotions	< 0.001	0.760
Sexual Problem	Positive Emotions	< 0.001	-0.499
	Negative Emotions	0.008	0.318
Positive Emotions	Negative Emotions	0.003	0.388

The study found that a strong positive correlation exists between high cognitive function and daily activities, whereas sexual issues demonstrate the least positive correlation with negative emotions. On the contrary, sexual engagement exhibits the most pronounced negative correlation with positive emotions, whereas social interactions have the least negative correlation with sexual problems. This suggests that individuals with high cognitive function also enhance daily activities positively, and those who engage in frequent sexual activity positively affect negative emotions. Nonetheless, individuals facing significant sexual challenges adversely influence positive emotions, while those highly involved in social activities detrimentally affect their sexuality.

DISCUSSION

Prevalence and Clinical Aspect

Chromosome analysis plays a crucial role in the accurate diagnosis and treatment of patients, particularly in cases of primary amenorrhea, and can contribute significantly, ranging from 16% to 50%, to the diagnosis of MRKH syndrome[16]. The MRKH syndrome anomaly is a condition that is seldom encountered and categorized as a form of rare disease by the National Institutes of Health[5]. This rare condition is proven by research by Kwon et al.[17] In South Korea for 22 years which found 27 MRKH syndrome patients out of 1,212 amenorrhea patients.

Cytogenetic examinations, supported by ultrasound scans, enable the classification of patients with suspected MRKH syndrome into two types (MRKH Type I and Type II), with ultrasound serving as the primary diagnostic method. Magnetic resonance imaging (MRI) and laparoscopy are also commonly employed for MRKH syndrome diagnosis, with MRI presenting several advantages over ultrasound, especially for more thorough evaluations[18]. In Indonesia, economic constraints make MRI examinations difficult for patients. However, a collaborative study[7] revealed genetic variations associated with MRKH syndrome, including LRP10, FRAS1, ESCO1, RSPO4, NPHP3, which can be detected using ultrasound alone. When ultrasonography (USG) results are ambiguous, undergoing magnetic resonance imaging (MRI) is advised due to challenges in accurately visualizing uterine tissue, Mullerian structures, or ovaries[19].

Clinical examinations, notably external genitalia assessment, play a pivotal role in diagnosing primary amenorrhea. However, there is a lack of research on clinical evaluations such as labia minora agenesis. In Indonesia, clinicians manage cases of labia minora agenesis or vaginal introitus with neo-vaginoplasty surgery, aiming to create a functional vagina to facilitate sexual activity. Vaginoplasty procedures, whether surgical or non-surgical, are employed for vaginal reconstruction like McIndoe and Davydov. McIndoe or laparotomic Davydov vaginoplasty methods are considered safe and effective for this purpose[9,20]

Baby et al.'s study on MRKH syndrome found that circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were normal in hormonal profile examinations. However, abnormalities in hormone levels, like elevated FSH, can result in various diagnoses, including gonadal dysgenesis[21,22]. Genetic screening remains essential for MRKH syndrome, particularly focusing on genes associated with anorectal and renal development..

Quality of Life in Women with Primary Amenorrhea and Uterovaginal Agenesis

Only 70 out of 100 eligible patients agreed to complete the questionnaire, citing challenges such as incorrect contact information, address or phone number changes, and varying levels of willingness among patients. There are multiple factors contributing to patients being unavailable for interviews, such as scheduling conflicts, changes in patients' preferences, and inconsistency in returning calls. Additionally, privacy concerns deter some individuals from sharing personal information with unfamiliar individuals[23].

Health-related quality of life (HRQoL) is influenced by both illness and medical interventions, reflecting how individuals or groups perceive their physical and mental well-being over time. Assessments of HRQoL should include aspects of well-being that reflect positive evaluations of social, psychological, and spiritual dimensions of life[24]. Statistical data highlights ongoing challenges for MRKH syndrome patients regarding sexuality, impacting psychological well-being, quality of life, and sexual function. These challenges include difficulties in sexual relationships, employment hurdles due to treatment, and concerns about infertility. However, several studies have shown improvements in patients' quality of life, psychological well-being, and sexual function post-treatment. Furthermore, direct comparisons of different treatment modalities are available, evaluating their effects on psychology, sexual function, and quality of life[25].

Women with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome are born without a uterus and vagina. Besides surgical interventions such as vaginal reconstruction, educating patients about psychosocial aspects is crucial. This education enables affected women to participate in sexual activities, build intimacy, and experience pleasure. Addressing the psychological and social challenges linked to this genetic condition necessitates support from genetic counselors to improve patients' quality of life. Exploring the psychological implications and creating patient-centered care strategies are essential for addressing these significant challenges that cannot be ignored[26,27].

Before considering sexual relationships and pregnancy, women with MRKH should receive comprehensive genetic counseling. Treatment primarily focuses on addressing vaginal agenesis by creating a functional neovagina. Over the past century, various surgical and non-surgical methods have been proposed to enable the

creation of a vagina suitable for sexual intercourse[28]. Furthermore, research has been conducted on fertility options for MRKH syndrome patients such as gestational surrogacy (GS) and uterine transplantation (UTx)[29]. Fontana stated that Huet et al. reviewed 13 cases of uterine transplantation, primarily among MRKH patients, to assess its viability for women with uterine infertility. However, only a small number of successful pregnancies following uterine transplantation have been documented among MRKH patients[30].

In this study, the psychological impact is highly significant on the patient's quality of life as a strong diagnosis of infertility can lead to feelings of disappointment, excessive anxiety, anger, uncertainty, and depression. The psychosocial consequences of MRKH are crucial aspects, as individuals must navigate challenges related to their body's different form, identity, and sexuality. Left unaddressed, patients may struggle to appreciate or feel pride in themselves[31]. High levels of sexual problems are linked to increased negative emotions and decreased positive emotions. Individuals experiencing sexual issues commonly report feelings of depression, anxiety, low self-esteem, and stress-related symptoms such as headaches and sleep disturbances. This decrease in positive emotions is attributed to lower levels of oxytocin hormone, which typically elicit feelings of happiness, satisfaction, and love[32]. Participating in social activities can decrease sexual issues among individuals. This is because these activities produce a range of emotions, including positive ones, and provide support, foster safety, and alleviate anxiety associated with sexual concerns[33].

CONCLUSION

The complex interplay among cognitive function, daily activities, sexual activities, and emotions unveils intriguing patterns. Females affected by MRKH syndrome encounter challenges in improving their quality of life, especially regarding sexuality. Enhanced cognitive function generally improves daily activities, while greater engagement in sexual activities tends to decrease negative emotions.

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