CHAPTER1

INTRODUCTION

1.1. Background

Primary amenorrhea defined as failure of menarche, associated with undeveloped secondary sexual signs by age of 13 years, or failure of menarche with well-developed secondary sexual signs by the age of 16 years.[1] It is a symptom that caused by different disorders.[2,3] To know the causes of primary amenorrhea, the initiation process of menstrual cycle should be understood. Menstrual cycle process needs an intact hypothalamo-hypophyseal axis, active ovaries, intact uterus with competent endometrium that can respond to hormones, and normal external genitalia as well.[1]

The world wide incidence estimated to be 1%,[4,5] and based on research results from different countries, there was no evidence for higher frequency in a specific population or ethnic group.[3] World Health Organization (WHO) ranked the primary amenorrhea as the sixth most common cause of infertility, hence the amenorrhea account 20% of all patients of infertility.[6]

Etiological factors of primary amenorrhea are broad, including genetic causes, endocrinal disorder, anatomical defects and psychological factors. A number of studies indicate the frequency of primary amenorrhea based on the

causes including gonadal dysgenesis due to chromosomal abnormality as the largest cause accounting 45%, followed by 15% due to Mayer Rokitanski Kuser Hauser syndrome (MRKH), Hypothalamic Idiopathic Hypogonadotropic Hypogonadism (IHH) estimated to be account 15% of the primary amenorrhea causes. Complete androgen insensitivity syndrome (CAIS) assessed for 10% of all the patients,[7] imperforated hymen and transverse septum

hymen reported to be 5%,[8] while the remaining 5% is distributed among congenital adrenal hyperplasia (CAH) and ovarian insensitivity syndrome.[3]

Gonadal dysgenesis is the commonest cause of primary amenorrhea.[9] More than half of the primary amenorrhea patients, that are created by gonadal dysgenesis are a result of abnormal sex chromosome(X).[1]Turner syndrome (45, X classical Turner syndrome), 45, X/46,XX (Turner variants) or (mosaicism 45, X/46, XY) is the most common chromosomal anomaly causing primary amenorrhea. The physical characteristic of Turner syndrome including short stature, webbed neck, shield chest, increased carrying angle of the elbow. With hyper gonadotropic hypoestrogentic amenorrhea,[9] pure gonadal dysgenesis 46, XX and 46, XY(Swyer syndrome) which is reported to be account 9% of primary amenorrhea patients.[9] The (47, XXX) trisomy and female phenotype 47, XXY (Klinfelter syndrome) are seen in one patient of primary amenorrhea.[10] This indicates the strong role of chromosomal abnormalities in the cause of the primary amenorrhea.[6]

Mayer Rokitanski Kuser Hauser syndrome (MRKH) is a congenital absence of uterus and vagina, the affected individuals have a 46, XX karyotyping and a normal secondary sex characteristics.[11] Type A (MRKH) patients show Symmetric uterine buds and fallopian tubes. Type B (MRKH) shows asymmetric uterine buds and fallopian tubes and being associated with other congenital anomalies (skeletal, renal, ovarian, ear and cardiac).[11] Complete androgen insensitivity syndrome (CAIS), those patients have normal female external genitalia. They typically present at puberty with primary amenorrhea and sparse to absent pubic or axillary hair. The sexual identity and orientation are normal.[12]

Imperforated hymen presents with cyclic pain and primary amenorrhea. Physical examination often reveals a bulging hymen with a bluish hue. Some patients also present with dysuria, back pain and painful defecation, as well as primary amenorrhea.[13] This condition

must be differentiated from a low transverse vaginal septum. Transverse vaginal septum the clinical presentation is the same as the imperforated hymen.[14]

Hypothalamic Idiopathic Hypogonadotropic Hypogonadism (IHH) presenting with delayed or absent pubertal development, either due to a GnRH mutation or a GnRH deficiency, and primary amenorrhea. The most common phenotypic association is anosmia in Kallmanns syndrome (KS).[17] The rare causes of primary amenorrhea including insensitive ovarian syndrome which characterized by normal growth and development, with elevated gonadotropins levels.[18] Congenital adrenal hyperplasia is a rare cause of primary amenorrhea. The patients present with hirsutism and ambiguous genitalia due to high circulating levels of androgen which have a negative feedback mechanism on the hypothalamus-pituitary axis (HPO).

The evaluation of primary amenorrhea patients needs a hard work up including cytogenetic and molecular analysis to determine the underlying chromosomal anomalies that is frequently associated. The hormonal assay is important to determine the source of endocrinal disorder.

This study aims to find out the frequency and distribution of chromosomal abnormalities (numerical and structural), and clinical profile of primary amenorrhea patients. In this descriptive study, the clinical profile including Height, Weight, Tanner stage, Prader stage, dysmorphic features and karyotype results had been collected.

1.2. Research questions

1.2.1. General research question

What are the clinical and cytogenetic profiles of primary amenorrhea patients?

1.2.2. Specific research question

1. What are karyotype results of primary amenorrhea patients?

2. What are the clinical profiles of primary amenorrhea patients?

3. What are the causes of primary amenorrhea according to the karyotype results?

4. Whether the clinical criteria of primary amenorrhea patients can be matched with karyotype results using scoring system?

1.3. Research Purpose

1.3.1. General Research Purpose

To know the clinical and cytogenetic profiles of primary amenorrhea patients.

1.3.2. Specific Research Purpose

1. To provide the Karyotype results of primary amenorrhea.
2. To determine the clinical profile of primary amenorrhea patients.
3. To know the most frequent causes of primary amenorrhea according to the karyotype results.
4. To detect the clinical criteria of primary amenorrhea patients and match it with the karyotype results using scoring system.

1.4. Research Advantages

1. To provide a good base for the researcher about chromosomal anomalies distribution and clinical features of primary amenorrhea patients.
2. To improve the knowledge of physicians and gynecology doctors for good evaluation of primary amenorrhea patients.
3. The result of this research can be a base for genetic counselor when they give counseling for primary amenorrhea patients

1.5. Research originality

Table 1. Research Originality

No	Author	Title of Publication	Method	Result
1	Merin T, Rema D, Preetha T, Amudha S, Jayalakshamma J and Mary M et al *(American journal of molecular and cellular biology* 2012)[2]	Amenorrhea: Cytogenetic Studies and Beyond	Karyotypes of female patients with amenorrhea referred from January 2006 to Jun 2012 were retrospectively analysed.	From 317 patients 41 had an abnormal karyotype. included 8 structural abnormalities,24 numerical abnormalities and 9 patients of 46, XY.
2	Osman M, Niglugin T, Eradal Tunc et al. *(Journal of Pediatric and adolescent Gynecology2014*)[17]	Frequency and types of chromosomal abnormalities in Turkish women with Amenorrhea	Chromosomal analysis was carried out on 393 patients with PA and SA Standard lymphocyte culturing procedure and karyotype was performed to all the patients	From 393 patients of PA and SA. Female karyotype detected in 337 patients (85%) and abnormal karyotype in 56 patients(14.2%) Turner syndrome detected in 39.3%(22/ 56) Structural abnormality (13/56) Male karyotype (19/ 56)
3	H. Afshar1, R. Najafipour2, J. Ansari2, N. Karimi3, M. Jalilvand2 et al (*journal of fundamental and applied sciences* 2016)[15]	Cytogenetic analysis in women with primary and secondary amenorrhea in Iran: Retrospective study on 110 patients.	Genotype phenotype correlation were performed on 110 patients with primary and secondary amenorrhea.	The Karyotype was normal in 91 patients (82.72%) and abnormal in19 patients (17.37%) .Monosomy X(6patients- 31.57%). The overall chromosomal abnormalities was between 15.9 % and 63.3%.
4	Tahir M. Malla, Fayaz A. Dar, Arshad A. Pandith, Mahrukh H. Zargar et al (*The Egyptian Journal of Medical Human Genetics*2015)[4]	Frequency and pattern of cytogenetic alterations in primary amenorrhea patients of Kashmir, North India	A total of 108 PA patients included in the study. Peripheral blood lymphocyte cultures were set for each subject, chromosomal analysis was carried out on well spread metaphases by the help of Cytovision software Version 3.9.	From 108 PA patients a70 (64.81%)had karyotype 46, XX while 38(35.18%) had abnormal karyotype. the numerical abnormalities were monosomy X, mosaic monosomyX (46 XX/45 XO) and sex reversal (46, XY). Structural abnormalities observed include isochromosome (46, XX, iXq), deletion (46, XX, delXq23-qter), duplication (46 XX, dup2q31).

This is the first study in Indonesia to provide the profiles of primary amenorrhea patients including the karyotype results and their clinical profiles. The new of this study that we made a scoring system and the patients had been distributed to match the scores according to their clinical criteria and then confirmed with their karyotype results. This scoring system needs further studies to measure validity and reliability, and wether it could be used as a clinical tool for rough prediction of karyotype results.