



Gonadotropin Levels and Underlying Diseases in Adolescent With Secondary Amenorrhea

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Purpose: To provide characteristics and hormonal profiles of secondary amenorrhea cases in adolescent patients treated at Hasan Sadikin General Hospital in Bandung.

Patients and Methods: The study was retrospective in nature and involved the analysis of medical records from 2017 to 2022 for 44 adolescent patients aged 10–18 who had secondary amenorrhea.

Results: There were 44 adolescents included in this study after excluded 69 adults from 113 secondary amenorrhea cases. The majority of patients were 14–17 years old (38.63%), in senior high school (45.45%), had started menarche at 11 years old (45.45%), had normal nutritional status (65.91%), and had normal stature (65.91%). The underlying diseases found in most patients were systemic lupus erythematosus (SLE) and tuberculosis. Among the patients, 29 had FSH, LH, and estradiol levels measured. The results of hormonal assays showed a wide range of abnormal serum levels, with normal to low concentrations of FSH and low levels of LH and estradiol. The median (interquartile range) results for FSH, LH, and estradiol were 4.57 (0.64, 90.65), 1.635 (0.06, 55.76), and 24.3 (0.2, 154.71), respectively. Positive significant correlation between FSH and LH ($p < 0.01$) was found in children with secondary amenorrhea.

Conclusion: Hormonal assay for FSH, LH, and Estradiol showed a wide range of abnormal serum level. Normal to low concentration levels of FSH and low LH and estradiol. The majority of secondary amenorrhea patients are associated with autoimmune disease and infection.

Keywords: adolescent, follicle-stimulating hormone, estradiol, luteinizing hormone, secondary amenorrhea, underlying disease

Introduction

Amenorrhea or loss of the menstrual cycle in adolescents can be divided into primary and secondary amenorrhea. If an adolescent patient does not menstruate until the age of 16 years with secondary sexual development or until the age of 14 years without secondary sexual development, the patient is considered to have primary amenorrhea, whereas secondary amenorrhea occurs in someone with normal menstrual periods but missing menstruation for 3 consecutive months or 6 months without regular menstruation.¹ Secondary amenorrhea is a problem affecting 3% to 5% of the female population annually.² The initial age for women to experience puberty is 8 years old with the secondary sexual development process started by thelarche (breast budding) followed by pubarche (pubic hair development), growth spurt and menstruation being the last developmental process.³

It is common for women within the first two years of menstruation and two years before menopause to experience anovulation and irregular cycle, especially for adolescents experiencing menstrual disorders or amenorrhea.¹ Pregnancy, lactation, and menopause are considered psychological causes of amenorrhea. Apart from these three things, amenorrhea can be caused by pathological conditions.⁴ The most common risk factor and cause of amenorrhea is pregnancy; pregnancy tests are essential for diagnosing amenorrhea. Other factors are stress, weight loss, and excessive physical activity.⁵

Amenorrhea occurs due to disruptions in the Hypothalamus-Pituitary-Ovarian (HPO) axis. The hypothalamus secretes GnRH that will stimulate the production of Gonadotropins (LH and FSH), leading to the synthesis of follicles and steroids, which subsequently causes sloughing of the endometrium. Disruption of this axis can cause an imbalance in hormone secretion that will lead to amenorrhea. Both primary and secondary amenorrhea have risk factors and causes and can be distinguished from the presence or absence of a history of menstruation. Thus, the causes of amenorrhea can be classified based on the location of the disorder; disorders in the hypothalamus, pituitary, anatomical disorders of the uterus and anovulatory factors.⁶

Secondary amenorrhea is a concerning issue in some female populations, particularly among adolescents, and thus, requires further attention. However, the lack of understanding regarding the underlying diseases and gonadotropin levels in patients with secondary amenorrhea at Hasan Sadikin hospital has prompted the authors to conduct research on this topic.

Materials and Methods

This is a retrospective analytical study, in which data was collected from the medical records of Hasan Sadikin General Hospital in Bandung during the period of 2017 to 2022. Baseline characteristics including age, education level, age of menarche, nutritional status, underlying diseases, treatment, levels of serum FSH, LH, estradiol, TSH and free T4 were collected. The study design is illustrated in Figure 1. The total sampling method was employed to determine the sample size. Between 2017 and 2022, there were 113 secondary amenorrhea cases which consisted of 44 adolescents aged 10 to 18 years old included in this study after separated 69 adults. Exclusion criteria included incomplete or lost medical records. Subject flow chart is depicted in Figure 2. Hasan Sadikin General Hospital is a top referral hospital in West Java Province. West Java Province has 26 regencies/cities, comprising 17 regencies and 9 cities, with 625 districts and 5877 villages. Hasan Sadikin General Hospital is one of teaching hospitals of Universitas Padjadjaran. This study has been authorized by the Health Research Ethics Committee of Hasan Sadikin General Hospital Bandung under the reference number LB.02.01/X.2.2.1/26349/2021 and conformed to the ethical guidelines of the Declaration of Helsinki.

The statistical analysis was facilitated using IBM[®] SPSS[®] version 26 software for the Windows 10 64-bit operating system and presented in the table. The subjects were anonymized and de-identified before analysis. Variables presented in frequency, percentage, mean, standard deviation and Pearson correlation test were used.

Results

Table 1 presents the most commonly observed age group was 14–16 years old (38.63%), followed by 17–18 years old (38.63%) and 10–13 years old (22.73%). Most of the patients were in Junior and Senior high school, had menarche at 11 years old, normal nutritional status and normal stature. The drug history of the patients was also recorded, with the

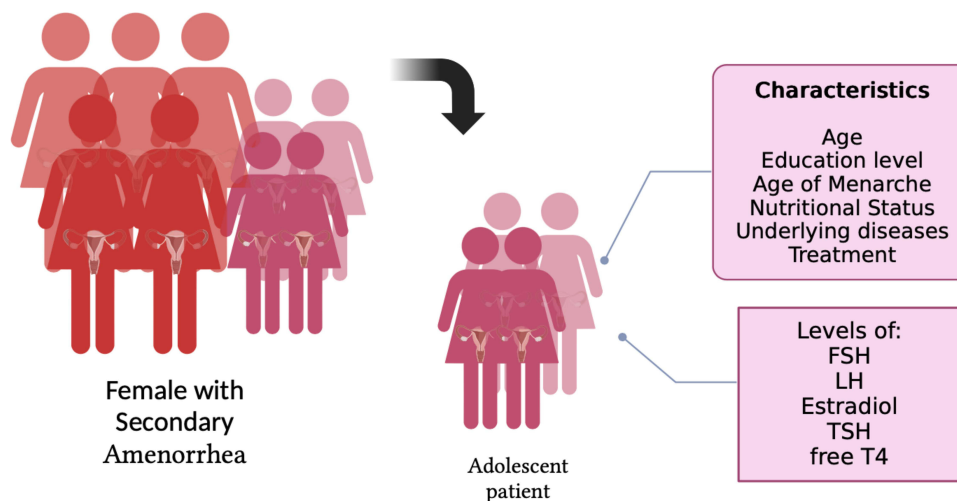


Figure 1 Study Design.

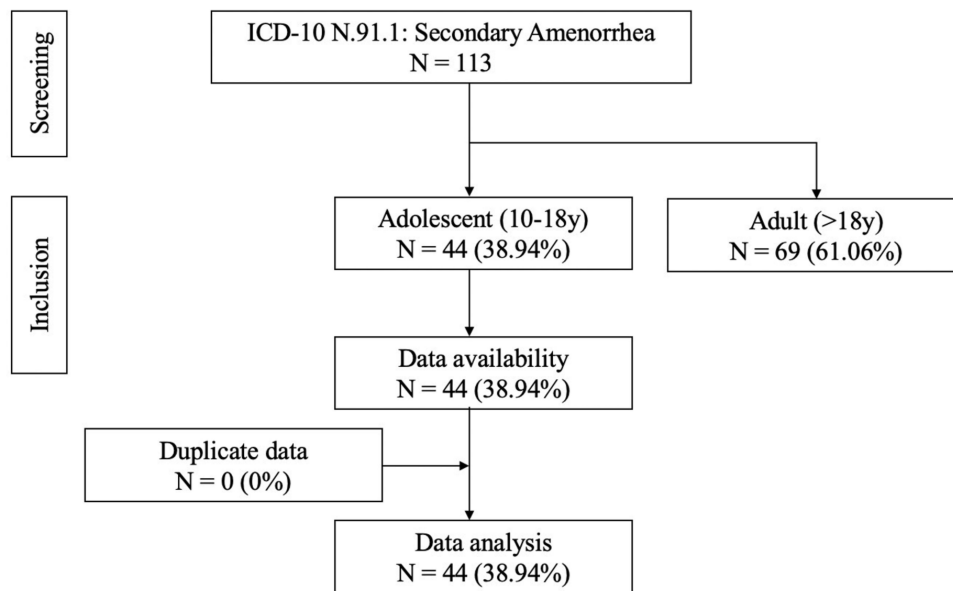


Figure 2 Prevalence of secondary amenorrhea patients based on age group and its availability in Hasan Sadikin Hospital's medical record period 2017–2022.

majority of them having consumed antibiotics (52.27%), while half of the patients (50%) were treated with corticosteroids. Nine patients (20.45%) received chemotherapy agents.

Table 2 presents the most common underlying diseases observed in secondary amenorrhea patients, with Systemic Lupus Erythematosus (36.36%) and Tuberculosis (31.82%) being the two most prevalent conditions.

Table 1 Characteristics of Secondary Amenorrhea Patients

Characteristic	Frequency	Percentage (%)	Mean	SD
Age			15.36	1.71
10–14 years old	10	22.73	13	0.48
14–17 years old	17	38.63	15.3	0.69
17–18 years old	17	38.63	17	0
Education				
Elementary school	6	13.63		
Junior high school	18	40.91		
Senior high school	20	45.45		
Age of Menarche				
9 years old	1	2.27		
10 years old	1	2.27		
11 years old	20	45.45		
12 years old	8	18.18		
13 years old	8	18.18		
14 years old	4	9.09		
15 years old	2	4.55		
Nutritional status				
Obese	1	2.27		
Overweight	1	2.27		
Normal	29	65.91		
Moderately underweight	5	11.36		
Severely underweight	8	18.18		

(Continued)

Table 1 (Continued).

Characteristic	Frequency	Percentage (%)	Mean	SD
Stature				
Tall Stature	0	0		
Normal	29	65.91		
Short Stature	15	34.09		
Treatment				
Antibiotic				
Yes	23	52.27		
No	21	47.73		
Corticosteroid				
Yes	22	50		
No	22	50		
Chemotherapy Agent				
Yes	9	20.45		
No	35	79.55		

Table 2 Underlying Diseases of Secondary Amenorrhea Patients

Diseases	Frequency	Percentage (%)
Systemic Lupus Erythematosus	16	36.36
Tuberculosis	14	31.82
T1DM	4	9.09
Osteosarcoma	2	4.54
Chronic Kidney Disease	1	2.27
Myelodysplasia Syndrome	1	2.27
Medulloblastoma	1	2.27
Primary hypothyroidism	1	2.27
Heart Failure	1	2.27
Wilms Tumor	1	2.27
Chron's Disease	1	2.27
Covid-19	1	2.27
Total	44	100

Out of 44 patients, only 29 had their hormone levels tested, with 15 individuals not being examined based on physician's assessment. [Table 3](#) and [Table 4](#) present the gonadotropin and estradiol profiles of the patients. In [Table 3](#), FSH, LH, and Estradiol levels were categorized into low, normal, or high levels based on follicular phase. [Table 4](#) categorizes FSH based on follicular phase and underlying disease. Out of the 29 patients, the majority of FSH hormone levels were found to be normal (41.38%) and low (34.48%). On the other hand, the serum levels of LH and Estradiol were predominantly low, with 58.62% and 51.72% of patients displaying low levels, respectively. Patients with Systemic Lupus Erythematosus (SLE) are distributed across two categories of FSH levels: low and normal. Meanwhile, patients with Tuberculosis are found in all three categories: low, normal, and high FSH levels.

A total of 10 patients with secondary amenorrhea's level of TSH and ft4 were collected, shown in [Table 5](#). One patient was diagnosed previously with primary hypothyroidism (10%). Most of the patient's level of TSH and ft4 (90%) were within the normal limit.

There was a positive significant correlation between FSH and LH ($p < 0.01$) in adolescent with secondary amenorrhea. However, there was no correlation between estradiol with FSH and LH ($p > 0.05$) ([Table 6](#)).

Table 3 Hormonal Profiles of Secondary Amenorrhea Patients

Hormone Median (IQR) Level	Group Range Based on Follicular Phase	Frequency N=29	Percentage (%)	Mean	SD
FSH 4.57 (0.64–90.65)	<2.5	10	34.48	1.53	0.58
	2.5–10.2	12	41.38	5	1.83
	>10.2	7	24.14	46.82	34.58
LH 1.635 (0.06–55.76)	<1.9	17	58.62	0.288	0.27
	1.9–12.5	7	24.14	5.63	2.96
	>12.5	5	17.24	48.57	6.54
Estradiol 24.3 (0.2–154.71)	<16.1	15	51.72	10.61	3.56
	16.1–238.3	14	48.28	44.48	22.91
	>238.3	0	0	0	0

Note: FSH: follicle stimulating hormone (mIU/mL), LH: luteinizing hormone (mIU/mL), Estradiol (pg/mL).

Table 4 Patient's Underlying Disease Based On FSH Level

FSH	Underlying Disease	Frequency N=29	Percentage (%)
Low	SLE	3	10.34
	Tuberculosis	3	10.34
	T1DM	2	6.89
	Medulloblastoma	1	3.45
	Osteosarcoma	1	3.45
Normal	SLE	4	13.79
	T1DM	2	6.89
	Tuberculosis	2	6.89
	Miscellaneous	4	13.79
High	Tuberculosis	5	17.24
	Heart Failure	1	3.45
	Myelodysplasia Syndrome	1	3.45

Note: Normal range based on follicular phase.

Table 5 Thyroid Profiles of Secondary Amenorrhea Patients

Thyroid Hormones	Groups	Frequency	Percentage (%)
TSH (μ lu/mL)	Low (<0.3)	0	0
	Normal (0.3–5)	9	90
	High (>5)	1	10
Free T4 (ng/dL)	Low (<0.7)	1	10
	Normal (0.7–1.8)	9	90
	High (>1.8)	0	0

Notes: TSH (thyroid stimulating hormone) and free T4 (thyroxine) were measured using Radioimmunoassay (RIA) and Immunoradiometric Assays (IRMA) techniques.

Discussion

It is common for half of the adolescent population to seek consultation within the first two years after menarche due to menstrual problems, which is often associated with the pubertal development process.⁷ This is attributed to the immaturity of the hypothalamic-pituitary-ovarian axis in adolescent females, leading to frequent menstrual issues.⁸ For a normal menstrual cycle, regular production of insulin, thyroid, ovarian, adrenal, and hypothalamus hormones is required. Any disruption in these circuits can interfere with the menstrual cycle's natural rhythm. In addition, endocrine disturbances such as diabetes, thyroid disease, and PCOS can also lead to menstrual problems.⁹

Table 6 Correlation Between FSH, LH, Estradiol in Children With Secondary Amenorrhea

		FSH	LH	Estradiol
FSH	Pearson Correlation	1	0.763**	0.053
	Sig. (2-tailed)		0.000	0.788
	N	28	28	28
LH	Pearson Correlation	0.763**	1	0.324
	Sig. (2-tailed)	0.000		0.093
	N	28	28	28
Estradiol	Pearson Correlation	0.053	0.324	1
	Sig. (2-tailed)	0.788	0.093	
	N	28	28	28

Notes: **Correlation is significant at the 0.01 level (2-tailed).

The study found that the majority of menarche (45.45%) in the adolescent population occurred at the age of 11 years old. This is consistent with a study conducted in Semarang, where the highest age of menarche was also found in 11-year-old children (34%). Earlier age of menarche was 9 years old.¹⁰

The study found that the most common underlying disease in secondary amenorrhea patients was SLE (36.36%). It is important to note that out of all cases of SLE, 10–20% are diagnosed as childhood-onset systemic lupus erythematosus (cSLE), and a case series reported that 11% of female cSLE who receive cyclophosphamide (CYC) under 21 years old have a risk of premature ovarian failure. CYC is known to cause gonadal toxicity and premature ovarian failure in adult patients, and although it is considered less common in cSLE patients, it is still a significant risk. Prepubertal children may have less gonadal toxicity since their gonads are in a quiescent stage and less exposed to hazardous medicines.^{11,12} Additionally, SLE can affect reproductive health even without treatment by CYC.¹³ While CYC as a chemotherapy agent can cause significant damage in a patient with secondary amenorrhea, SLE patients also have a higher chance of experiencing secondary amenorrhea than a healthy girl. This study reported 16 (36.36%) SLE patients, and 9 (20.45%) underwent chemotherapy treatment due to causes other than SLE.

Tuberculosis (TB) is another common underlying disease observed in patients with secondary amenorrhea, accounting for 31.82% of cases. The incidence of TB among adolescents and young adults aged 10 to 24 was reported to be 1.78 million globally in 2012.¹⁴ Non-genital tuberculosis can affect menstrual function through a complex network of interconnected processes involving hypothalamic-pituitary-ovarian function, although the underlying pathophysiology is not yet fully understood. According to several studies, abnormality in menstrual function may occur due to hypo-estrogenic hormone levels.¹⁵ For instance, a case report of a girl with disseminated TB showed hypothalamic hypogonadotropic amenorrhea with decreased FSH and LH levels, leading to decreased estrogen production.¹⁶

Four patients (9.09%) in this study were diagnosed with type 1 diabetes mellitus, which has been associated with amenorrhea and oligomenorrhea, and further research is needed to confirm this association. Menstrual disorders in diabetic patients may be caused by reduced LH secretion, delay in the positive estrogen loop, and the development of hyperandrogenism.¹⁷ Amenorrhea has also been observed in patients with type 2 diabetes, which has been linked to insulin resistance in polycystic ovary syndrome (PCOS).¹⁸ In a study, PCOS was found to be associated with IR and other metabolic disorders, although no genetic link has been established.¹⁹ Another underlying disease observed in one patient (2.27%) was hypothyroidism, which can increase prolactin levels along with thyrotropin-releasing hormone (TRH). High levels of TRH and hyperprolactinemia in primary hypothyroidism patients can lead to amenorrhea.²⁰ Besides the one individual who had already been diagnosed with hypothyroidism, the thyroid function of the other nine examined patients yielded results within normal limits.

Adolescents commonly experience menstrual irregularities such as hypo menstrual syndrome, dysmenorrhea, and amenorrhea, as found in a study conducted in Ukraine. This study also discovered a significant association between thyroid dysfunction and hypomenorrhea (shortened menstrual bleeding) as well as between thyroid function and amenorrhea.²¹ Therefore, endocrine problems such as thyroid dysfunction and hyperandrogenism should also be taken

into account as potential causes of menstrual irregularities in adolescents.²² However, in this study, limited number of thyroid profile of subjects were checked revealed within normal limit (9 from 10 patients have normal thyroid function). Additionally, chronic kidney disease was identified in 1 (2.27%) patient in this study. While a study conducted in Aceh did not find a relationship between secondary amenorrhea and the duration of therapy for chronic kidney failure, it was found to be more related to disruption of reproductive hormones, uremia syndrome, and psychological factors.²³

Although most of the patients in this study had normal nutritional status, a considerable number of patients (18.18%) were severely underweight, and 11.36% were moderately underweight. Children with chronic diseases are more susceptible to malnutrition due to increased caloric requirements, malabsorption, altered nutrient utilization, and limited nutrient availability due to fluid status and feeding tolerance.²⁴ These chronic or diseases can also interfere with linear growth and, in severe cases, lead to growth failure and short stature.²⁵ In fact, 34.09% of the patients in this study were found to have short stature. In addition to the underlying diseases discussed earlier, this study also identified other common chronic conditions in children, including cardiac diseases, malignancy, anemia, and renal disease, which were present in 2.27% of patients.

The hormonal profiles of the patients showed that a majority had abnormal hormone levels, with many showing low levels of LH and estradiol, and some showing low levels of FSH. LH and FSH work together in regulating reproductive function, and low levels of LH in both men and women can indicate various underlying issues such as anorexia, pituitary gland problems, stress, or hypothalamus injury. In cases where LH levels are lower than FSH, it is usually diagnosed as functional hypothalamic amenorrhea. Estradiol is an important hormone for bone health, and its levels are often monitored during therapy to prevent bone loss.²⁶ Hypothalamic amenorrhea might be the underlying cause for most of the patients in this study with chronic diseases. Several theories have postulated chronic or systemic diseases cause nutritional deficiencies resulting in negative energy balance or chronic inflammatory states that lead to functional hypogonadotropic hypogonadism.²⁷

This study was conducted in Central Referral Hospital in West Java Indonesia, which limits its generalizability to other populations and settings. The sample size was also relatively small, which may affect the accuracy and reliability of the results. This study requires a more extensive study, including larger and more diverse samples, to confirm the associations and findings presented in the current study. There may be potential biases or confounding factors in this retrospective study which could affect the study's findings. The study did not include information on lifestyle factors, such as exercise and diet, which could also impact menstrual irregularities. Finally, the study did not investigate the long-term outcomes of patients, such as the development of osteoporosis or fertility issues.

Conclusion

In conclusion, this study found that the majority of patients with secondary amenorrhea at Hasan Sadikin General Hospital in Bandung had underlying autoimmune diseases or infections. The hormonal laboratory examination of FSH, LH, and estradiol revealed a wide range of abnormal serum levels, with normal to low levels of FSH and low levels of LH and estradiol. Most of the subjects have normal thyroid function. These findings suggest the need for further investigation into the potential causes of secondary amenorrhea in this patient population, as well as the development of appropriate treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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