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Causes of Secondary Amenorrhea: A report of 437 cases in Thailand

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ABSTRACT

Objectives: The aim of this study was to determine the prevalence of etiologic causes of secondary amenorrhea in Thailand.

Materials and Methods: A retrospective study was performed using 437 complete medical records of women with secondary amenorrhea who visited the Gynecologic Endocrinology clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand from April 1999 to October 2020.

Results: At the time of registration at our clinic, the patients had an average age of 28.7 ± 7.7 years. The median duration of amenorrhea was 8 months (range three months to 228 months). The majority of patients were nulliparous (70%). The average body mass index (BMI) was 25.2 ± 6.7 kg/m^2. More than half of all patients were overweight (11.2%) and obese (42.6%). Patients with polycystic ovary syndrome (PCOS) had the highest BMI. The four most common causes of secondary amenorrhea were PCOS (30.2%), anovulation (27.2%), hyperprolactinemia (9.8%), and premature ovarian insufficiency (9.2%). Other etiologies were diverse and less frequent. Two thirds of etiologies of secondary amenorrhea were in compartment four (67.5%). The prevalence of causes of secondary amenorrhea in compartment two (9.2%) and three (10.1%) was similar. The uterine cause and outflow tract obstruction was the least common cause of secondary amenorrhea (8.0%) of all four compartments. Postpill amenorrhea was found in 6.4% of patients. Meanwhile, thyroid disorder was the cause of secondary amenorrhea in 5% of patients.

Conclusion: The most common causes of primary and secondary amenorrhea were different. The most common cause of secondary amenorrhea in this study was PCOS. Further studies are required to determine the difference in causes of secondary amenorrhea in different nations.

Keywords: secondary amenorrhea, polycystic ovary syndrome, anovulation, hyperprolactinemia, premature ovarian insufficiency.

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สาเหตุของภาวะขาดระดูชนิดทุติยภูมิ: รายงานผู้ป่วย 437 รายในประเทศไทย

มุกประดับ ดารกมาศ, ประสงค์ ตันมหาสมุทร, กิติรัตน์ เตชะไตรศักดิ์, มณี รัตนไชยานนท์, สุชาดา อินทวิวัฒน์, ธันยารัตน์ วงศ์วนานุรักษ์, ปณิชา จันทราพานิชกุล และณิชมน ปิงกุล

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาความชุกของสาเหตุต่าง ๆ ของภาวะขาดระดูทุติยภูมิในประเทศไทย*

วัสดุและวิธีการ*: การศึกษาเชิงพรรณนาโดยการสืบค้นเวชระเบียนของสตรีที่มีภาวะขาดระดูทุติยภูมิ 437 คน ที่มารับการตรวจที่คลินิกต่อมไร้ท่อทางนรีเวช ภาควิชาสูตศาสตร์ นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล ประเทศไทย ตั้งแต่เดือนเมษายน พ.ศ. 2542 ถึงเดือนตุลาคม พ.ศ.2563*

ผลการศึกษา*: อายุเฉลี่ยของผู้ป่วย 28.7 ± 7.7 ปี ค่ามัธยฐานของระยะเวลาที่ขาดระดูเท่ากับ 8 เดือน (ช่วงระหว่าง 3 - 228 เดือน) ผู้ป่วยส่วนใหญ่ยังไม่มีบุตร (ร้อยละ 70) ดัชนีมวลกายเฉลี่ยเท่ากับ 25.2 ± 6.7 กิโลกรัมต่อตารางเมตร ผู้ป่วยจำนวนมากกว่าครึ่งหนึ่งมีน้ำหนักตัวเกิน (ร้อยละ 11.2) และอ้วน (ร้อยละ 42.6) ผู้ป่วยในกลุ่มอาการถุงน้ำรังไข่หลายใบมีดัชนีมวลกายสูงที่สุด สาเหตุของภาวะขาดระดูทุติยภูมิที่พบบ่อยที่สุด 4 อันดับแรก ได้แก่ กลุ่มอาการถุงน้ำรังไข่หลายใบ (ร้อยละ 30.2) ภาวะไม่ตกไข่ (ร้อยละ 27.2) ภาวะโปรแลกตินในเลือดสูง (ร้อยละ 9.8) และภาวะรังไข่ทำงานบกพร่องก่อนวัย (ร้อยละ 9.2) สาเหตุอื่น ๆ พบได้น้อย สองในสามของสาเหตุของภาวะขาดระดูทุติยภูมิอยู่ในคอมพาร์ตเมนท์สี่ (ร้อยละ 67.5) ความชุกของสาเหตุของภาวะขาดระดูทุติยภูมิในคอมพาร์ตเมนท์สอง (ร้อยละ 9.2) และคอมพาร์ตเมนท์สาม (ร้อยละ 10.1) ใกล้เคียงกัน คอมพาร์ตเมนท์ที่มีสาเหตุจากมดลูกและการอุดกั้นของทางออกพบได้น้อยที่สุด (ร้อยละ 8) ภาวะขาดระดูหลังหยุดยาคุมกำเนิดพบได้ ร้อยละ 6.4 ความผิดปกติของไทรอยด์พบเป็นสาเหตุของภาวะขาดระดูทุติยภูมิได้ร้อยละ 5*

สรุป*: สาเหตุที่พบบ่อยของภาวะขาดระดูปฐมภูมิและทุติยภูมิแตกต่างกัน สาเหตุของภาวะขาดระดูทุติยภูมิที่พบได้บ่อยที่สุดในการศึกษานี้คือกลุ่มอาการถุงน้ำรังไข่หลายใบ ควรทำการศึกษาเพิ่มเติมถึงสาเหตุของภาวะขาดระดูทุติยภูมิในประชากรที่มีเชื้อชาติแตกต่างกัน*

คำสำคัญ*: ภาวะขาดระดูทุติยภูมิ, กลุ่มอาการถุงน้ำรังไข่หลายใบ, ภาวะไม่ตกไข่, ภาวะโปรแลกตินในเลือดสูง, ภาวะรังไข่ทำงานบกพร่องก่อนวัย*

Introduction

Secondary amenorrhea is defined as no menses for a time interval of at least three previous cycles or no menses over a six-month period[1]. The diagnoses of primary and secondary amenorrhea differ. However, some conditions present as primary or secondary amenorrhea such as premature ovarian insufficiency (POI), polycystic ovary syndrome (PCOS), hyperprolactinemia, and pregnancy. A functioning hypothalamic-pituitary-ovarian (HPO) axis along with a normal genital outflow tract and uterus is required for menstrual function. Any disruption or abnormality to the organ can result in amenorrhea. The causes of amenorrhea can be categorized according to the site or level of disorder as compartment I-IV.

A careful review of patient history and physical examination is necessary to appropriately investigate, diagnose, and treat secondary amenorrhea. Laboratory investigations are based on data from the medical history and physical examination[1].

A few reports on the causes of secondary amenorrhea have been published. In 1986, Reindollar et al shared the results of a study in which 262 American patients had adult-onset amenorrhea[2]. This study showed that hypothalamic suppression followed by chronic anovulation, and then hyperprolactinemia and ovarian failure were the most frequently encountered etiologies. Another large case series by Kwon et al in 2014 showed that PCOS, POI, and nutrition-related hypogonadotropic hypogonadism were the three most common causes of secondary amenorrhea in Korean patients[2]. Since there is a difference in the cause of secondary amenorrhea between Western and Eastern populations, the aim of this study was to determine the prevalence of etiologic causes of secondary amenorrhea in Thailand.

Materials and Methods

This retrospective study was carried out at the Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The study protocol was approved by the Siriraj Institutional Review Board (SIRB) (certificate of approval no. Si 299/2021). Our study's anonymous retrospective design negated the need to obtain written informed consent from the participants.

The sample size was calculated using a formula to estimate a single proportion. When the precision was 0.05, α = 0.05, and the prevalence of PCOS among women presenting with secondary amenorrhea from the study by Kwon et al was 48.4%[2], the sample size plus 10% allowance for incomplete data was 422.

We reviewed the medical records of 865 women with secondary amenorrhea who registered at our clinic between April 1999 and October 2020. Of this group, complete medical histories and physical examinations for adequate investigation for diagnosis was available for 437 cases who then became eligible for this report.

The process of secondary amenorrhea diagnosis at our institute was conducted as follows: 1. Review of patient history, including the chief complaint, present condition, and past and family history, 2. Physical examination, including general examination and rectal and/or pelvic examination (PR/PV), 3. Laboratory investigations: Urine pregnancy test to rule out pregnancy if indicated. Serum thyroid stimulating hormone (TSH) and prolactin was the initial laboratory test along with the progestin challenge test. Further investigations depended on results

from the initial step, including estrogen- progestin challenge test, serum follicle stimulating hormone (FSH), estradiol, total testosterone, pelvic ultrasonography, saline infusion sonohysterography, imaging of pituitary and hypothalamus, karyotype, and autoimmune status.

According to the revised Rotterdam 2003 criteria[3], PCOS is diagnosed if two of the following criteria are met: clinical and biochemical signs of hyperandrogenism, oligo or anovulation, and polycystic ovaries on ultrasonography. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumor, and Cushing syndrome, must be excluded. Before the Rotterdam 2003 criteria, we diagnosed PCOS using the following criteria: chronic anovulation and clinical and/or biochemical signs of hyperandrogenism, and exclusion of other etiologies.

Statistical analysis

All data analysis was performed using SPSS Statistics for Windows version 17 (SPSS, Inc., Chicago, IL, USA). The outcomes were reported as frequency and percentage. The Kolmogorov-Smirnov test was used to test the distribution of continuous data. Normally, distributed continuous data was presented as mean ± standard deviation (SD), and non-normally distributed continuous data was given as median and range.

Results

A total of 437 patients were eligible for the present study. By the time of registration at our clinic, the average age of patients was 28.7 ± 7.7 years. The average body mass index (BMI) was 25.2 ± 6.7 kg/m^2. More than half of all patients were overweight (11.2%) and obese (42.6%). Patients with PCOS had the highest BMI. The median duration of amenorrhea was eight months (range three months-228 months). The majority of the patients were nulliparous (70%).

Table 1 demonstrates the causes of secondary amenorrhea and clinical features of patients. The four most common causes were PCOS (30.2%), followed by anovulation (27.2%), hyperprolactinemia (9.8%) and POI (9.2%). Other etiologies were diverse and less frequent. Two thirds of the etiologies of secondary amenorrhea were in compartment four (67.5%). The prevalence of the causes of secondary amenorrhea in compartment two (9.2%) and three (10.1%) were similar. Uterine cause and outflow tract obstruction was the least common cause of secondary amenorrhea (8.0%) of all the four compartments. Tuberculous endometritis was found in one patient.

Most causes related to POI were idiopathic (60%), and they were attributed to chemotherapeutic agents, ovarian operation, chromosome abnormality, and autoimmune disease. The patients with autoimmune disease included systemic lupus erythematosus (7 cases), autoimmune thyroiditis (2 cases) and Wegener granulomatosis (1 case).

Hyperprolactinemia was the most common cause in compartment three. Meanwhile, the most common cause of hyperprolactinemia was drug induced hyperprolactinemia (41.9%). Pituitary adenoma was found in 32.6% of hyperprolactinemic patients. One patient with craniopharyngioma developed panhypopituitarism after tumor removal.

Postpill amenorrhea was found in 6.4% of patients. Meanwhile, thyroid disorder was the cause of secondary amenorrhea in 5% of patients.

Table 1. The causes of secondary amenorrhea and clinical features of patients.

Cause	Number (%)	Age at registration (years)	BMI (kg/m²)	Duration of amenorrhea (month)	
		mean ± SD	mean± SD	median	[min, max]
Compartment 1	**35 (8.0)**				
Cervical stenosis	19 (4.3)	31.1 ± 5.4	24.1 ± 3.8	9	[3, 117]
Uterine synechiae	16 (3.7)	32.1 ± 6.4	22.1 ± 3.1	12	[3, 120]
Compartment 2	**40 (9.2)**				
Premature ovarian insufficiency	40 (9.2)	32.0 ± 6.5	21.6 ± 3.5	12	[3, 120]
Idiopathic	24 (5.5)	32.4 ± 5.8	20.8 ± 2.7	10	[3, 120]
Chemotherapy induced	2 (0.5)	30 ± 15.6	25.6 ± 7.7		[8, 36]
Ovarian surgery related	2 (0.5)	38 ± 0.0	23.8 ± 2.1		[4, 6]
Autoimmune	10 (2.3)	32.5 ± 7.1	22.6 ± 4.2	18	[3, 60]
Chromosomal abnormality (47,XXX and 46,XX9qh+)	2 (0.5)	26.0 ± 2.8	20.4 ± 3.8		[7, 36]
Compartment 3	**44 (10.1)**				
Hyperprolactinemia	43 (9.8)	29.5 ± 7.5	24.8 ± 5.4	7	[3, 120]
Pituitary adenoma	14 (3.2)	31.4 ± 5.8	24.7 ± 5.4	12	[4, 108]
Drug induced	18 (4.1)	27.5 ± 8.5	24.2 ± 4.8	5.5	[3, 36]
Idiopathic	11 (2.5)	30.6 ± 7.5	25.6 ± 6.9	12	[3, 120]
Panhypopituitarism	1 (0.2)	20	27.3	24	
Compartment 4	**295 (67.5)**				
Polycystic ovary syndrome	132 (30.2)	24.8 ± 6.5	28.3 ± 8.1	7	[3, 228]
Anovulation	119 (27.2)	29.1 ± 8.3	25.0 ± 7.2	8	[3, 228]
Stress related	4 (0.9)	27.3 ± 10.5	20.3 ± 4.1	6	[3, 12]
Weight changes related	37(8.5)	27.8 ± 7.0	27.8 ± 8.5	10	[3, 72]
Chronic disease	11 (2.5)	30.9 ± 10.8	24.2 ± 6.9	12	[3, 60]
Idiopathic	67 (15.3)	29.5 ± 8.3	23.6 ± 5.5	7	[3, 228]
Hypogonadotropic hypogonadism	17 (3.9)	29.9 ± 7.0	22.6 ± 5.6	12	[3, 96]
Postpill amenorrhea	28 (6.4)	31.9 ± 6.5	24.7 ± 5.8	5	[3, 12]
Other	**22 (5.0)**				
Hypothyroidism	16 (3.7)	35.7 ± 7.0	24.1 ± 3.2	7	[3, 48]
Hyperthyroidism	6 (1.4)	28.3 ± 9.4	22.9 ± 2.6	11	[6, 84]
Total	**437 (100%)**	28.7 ± 7.7	25.2 ± 6.7	8	[3, 228]

Data are presented as mean ± standard deviation, median (interquartile range), or number (percent) and [95% confidence interval].
Data were analyzed using: (a) one-way analysis of variance; (b) Kruskal-Wallis H, or (c) Chi-square test.
Each patient might experience more than one adverse event.
CI: confidence interval, BMI: body mass index

Discussion

This study evaluated the etiologies of secondary amenorrhea in 437 patients. The four most common causes of amenorrhea were PCOS (30.2%), anovulation (27.2%), hyperprolactinemia (9.8%), and POI (9.2%). This contrasts with our earlier study of 295 women with primary amenorrhea in which the most common etiologies were Müllerian agenesis, gonadal dysgenesis, and hypogonadotropic hypogonadism[4]. The difference in etiologies between primary and secondary amenorrhea was consistent with results of the American and Korean

studies[2, 5]. However, the frequency and order of etiology in our study was different.

As seen in the Korean study[2], PCOS was the most common cause of secondary amenorrhea in our study. However, the prevalence of PCOS in our study was lower than in the Korean series (30.2% vs 48.4%). In addition, other common causes differed as well. The second and third most common causes in the Korean study were POI (14.0%), and nutrition-related hypogonadotropic hypogonadism (8.3%). The average age at registration in the Korean study was 24.6 years, which was younger than in this study.

However, both studies were in contrast to a 1986[2] study by Reindollar et al, which revealed that the four most common causes of secondary amenorrhea in the American population were hypothalamic suppression (33.5%), chronic anovulation (28%), hyperprolactinemia (14%), and ovarian failure (12%). Hypogonadotropic hypogonadism was found in only 3.9% of patients in this study and 8.3% in the Korean study. More than half of American patients (54%) had hypogonadism while only 13% and 22% had the condition in this study and the Korean study. The second to fourth most common etiologies in the American study had a similar frequency and order to observations in this study. Postpill amenorrhea occurred in 29% of all patients in the American study, which seemed high and was more than the observation in this study (6.4%). The average age of presentation in the American study and our study was similar (26.4 vs 28.8 years). In the American study, the authors included PCOS into the chronic anovulation group. The most common cause of hypothalamic suppression in the American and Korean studies was associated to anorexia nervosa and weight loss[2, 5]. Only three patients with anorexia nervosa were found in this study. This difference may be due to variations in prevalence of anorexia nervosa, socio-cultural influences that focus on body image and weight in young women[6, 7], and also physical and emotional stressors[8].

PCOS is characterized by menstrual disturbances, ranging from abnormal uterine bleeding to oligomenorrhea and amenorrhea, hyperandrogenism, and infertility. PCOS patients are more likely to present with oligomenorrhea (76%) than amenorrhea (24%)[9, 10]. The symptoms often occur first at menarche, but signs of androgen excess may not become evident until several years later and these signs increase over time[11].

In North America, 75% of women with PCOS are obese[12], while 6.8% and 58.3% of patients with PCOS in this study were overweight and obese, respectively.

Consistent with the American and Korean series[2, 5], the prevalence of an abnormal karyotype in POI of secondary amenorrhea appeared low compared to cases of gonadal dysgenesis causing primary amenorrhea[4]. Most causes related to POI were idiopathic, and attributed to chemotherapeutic agents, ovarian operations and autoimmune disease[13, 14]. Autoimmune disease related to POI in Korean study and our study was similar[2].

Hyperprolactinemia was the most common cause of secondary amenorrhea in compartment three. Hyperprolactinemia was 14% in the American series[5] and 7.8 % in Korean series[2], which was quite similar to the 9.8% noted in this study. In our study, the most common cause of hyperprolactinemia was drug induced hyperprolactinemia (41.9%). Pituitary adenoma was found in 32.6% of hyperprolactinemic patients. Thyroid disorder was reported as 1.5% in both the American and Korean series[2, 5], but was 5% in our study. The data provides support for the practice of obtaining a serum prolactin and TSH determination in women with amenorrhea. Serum prolactin and TSH combined with the progestin challenge test is the appropriate initial investigation for secondary amenorrhea.

Secondary amenorrhea has a significantly less impact on future well-being than was reported for patients whose amenorrhea developed as a result of pubertal aberrancy. The etiologies of secondary amenorrhea were largely different from those of primary amenorrhea. Analysis of morbidity data

indicated that secondary amenorrhea presents less significant detrimental effects on the quality of life, including fertility, than primary amenorrhea[5, 15]. However, early diagnosis, treatment, and counseling remain essential for all patients.

This study has some mentionable limitations. First, the present study was a retrospective chart review, which is a study design known to be associated with missing and/or incomplete data. Second, the study was conducted in a tertiary care university hospital, and thus, the study population was affected by patient's preference, referral patterns, and what referring physicians were comfortable taking care of.

Conclusion

In conclusion, the most common causes of primary and secondary amenorrhea are different. The most common cause of secondary amenorrhea in this study was PCOS, which was similar to the Korean study[2], but contrasts the American study[5]. Thus, ethnic, environmental, socio-cultural, and genetic factors may play a role in the development of amenorrhea. Further studies are required to determine the difference in causes of secondary amenorrhea in different nations.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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