Primary Amenorrhoea : A Retrospective Study at Siriraj Hospital

MANEE RATTANACHAIYANONT, M.D.*,
SURASAK ANGSUWATTANA, M.D.*,
ORAWAN MEKMAHAN, M.D.*,
SOMBOON KUNATHIKOM, M.D.*,
KITIRAT TECHATRAISAK, M.D.*,
CHARUNEE KARAVAGUL, M.D.*,
SOMCHIT KO-ANANTAKUL, M.D.*

Abstract

To determine the incidence of etiologic factors responsible for primary amenorrhoea in Siriraj Hospital on the basis of clinical examination and laboratory investigations. A retrospective study was performed from the records of patients who attended the Reproductive Endocrine Clinic at Siriraj Hospital from 1 September 1992 to 31 August 1995. During the 3 years of the study period, there were 110 cases of primary amenorrhoea. One hundred and one cases were analyzed: nine cases were excluded because the patients lost follow-up before the final diagnosis could be concluded. The two most common etiologic factors were Mullerian agenesis (39.65%) and gonadal dysgenesis (32.69%). Mean age of the patients when they first consulted the physicians was 22.45 ± 6.06 years. Karyotyping was done on 28 of 32 cases of gonadal dysgenesis; 46,XX karyotype was found in 50 per cent and 45,XO in 14.29 per cent of analyzed cases. Clinical examination gave wrong diagnosis of absent uterus in 4 cases who were in the hypoestrogenic stage with hypoplastic uterus; ultrasonography and laparoscopy gave the wrong diagnosis in 1 case each in our report. These patients successfully menstruated after hormonal replacement therapy.

The incidence of etiologic causes and cytogenetic study of primary amenorrhoea in our study is different from earlier reports. Racial and environmental differences may play a role in these differences. The facilities of diagnostic tools may also play a part. However, both clinical examination and many laboratory investigations have to be completed before final diagnosis of etiologic causes of primary amenorrhoea are elucidated. Diagnosis based on inadequate data can be misleading.

Primary amenorrhoea is defined as the failure of menarche by the age of 16 in any girl or by the age of 14 in a girl who still does not have secondary sexual characteristics[1]. Primary amenorrhoea is not a definite disease but a symptom of various disorders. Although it is not a common symp-

* Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

tom, it pertains significant problems. Untreated amenorrhoea is associated with significant long-term morbidity, especially in young women who are the population at risk of primary amenorrhoea. Early recognition of the definite etiology and institution of the appropriate treatment will minimize late complications[2].

Although primary amenorrhoea has long been recognized and the literature on this problem is profuse, there are not many studies on large numbers of patients. The majority of papers are case-reports and some are based on a small series of patients[3]. Apart from this, the incidence of the diseases that cause this problem may vary from area to area due to different racial groups of patients. Since there are few large series on this topic from Asia, the present study was undertaken to determine the incidence of etiologic factors responsible for primary amenorrhoea in Siriraj Hospital on the basis of clinical examination and laboratory investigation.

MATERIAL AND METHOD

A retrospective study was performed from the medical records of patients who were referred to the Reproductive Endocrine Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. From 1 September 1992 to 31 August 1995, there were 110 patients who were diagnosed as having primary amenorrhoea. One hundred and one cases with a complete history, physical examination and adequate investigation were included for analysis. Nine cases were excluded because the patients lost follow-up before the final diagnosis could be concluded.

The work up of primary amenorrhoea patients in Siriraj Hospital composes of:

(1) History taking (Hx) includes chief complaint, present history, past history and family history.

(2) Physical examination (PE) includes general examination and rectal and/or pelvic examination (PR/PV). In case that PR/PV cannot give clear information about pelvic organs, transabdominal pelvic ultrasonography and/or diagnostic laparoscopy will be prescribed.

(3) Laboratory investigations (Ix) are ordered for three purposed: for diagnosis of the causes, for evaluation of the patient's status and for investigation of the associated disorder. Therefore, the Ix of each patient depends on the provisional diagnosis derived from Hx and PE.

The patients were classified into 5 groups based on the compartment of organs that were involved in the etiologic causes of amenorrhoea. They are:

Compartment 1: End-organ failure or outflow tract obstruction,
Compartment 2: Gonadal failure,
Compartment 3: Pituitary cause,
Compartment 4: Hypothalamic cause,
and other causes.

Karyotyping

The karyotype was determined using peripheral leukocyte culture and G-banding technic[4-6].

RESULTS

The three most common etiologic factors of primary amenorrhoea were Mullerian agenesis (39.65%), gonadal dysgenesis (32.69%) and hypogonadotropic hypogonadism (8%) respectively (Table 1).

Clinical features of the patients are shown in Table 1 and Fig. 1. Mean age of the patients when they first consulted the physicians was 22.5 $\pm$ 6.1 years; the oldest patient was a case of Mullerian agenesis (41 y/o) whereas the youngest was male pseudohermaphrodite with incomplete testicular feminization (14 y/o). The majority of the patients were single. There were 4 cases of Mullerian agenesis having sexual problems which led to divorce in 2 cases. The height of the patients was not clinically different among the five groups while Turner syndrome (45, XO and mosaic) was still the shortest. The development of secondary sexual characteristics were more advanced in the group with compartment-1 defect than the group with compartment-2 defect, however, there was an overlap in Tanner stage between the groups (Fig. 1).

Pelvic examination gave wrong diagnosis of absent uterus in 4 cases who were in the hypoestrogenic stage with hypoplastic uterus; ultrasonography gave wrong diagnosis in 1 case; laparoscopy also gave wrong diagnosis in 1 case. These patients successfully menstruated after hormonal replacement therapy (Table 2).

Karyotyping was done on 28 of 32 cases of gonadal dysgenesis; 46,XX karyotype was found in 50 per cent, mosaic in 35.71 per cent and 45,XO in 14.29 per cent of analyzed cases. Other diseases possessed normal karyotype (either 46,XX or 46, XY) except for a case of male pseudohermaphro-

Table 1. Clinical features of patients with primary amenorrhoea.

Causes	No.	Age when consulted (yr)		Height (cm)	Marrital status		
		mean ± SD	range		S	M	D
Compartment 1							
Transverse vaginal septum	1		19	ND	1	0	0
Tuberculous endometritis	1		35	ND	0	1	0
Mullerian anomaly				152.6 ± 7.1			
Absent endometruim	2	27.5 ± 16.3	16-39		0	2	0
Mullerian agenesis	40	22.4 ± 6.0	16-41		21	17 (a)	2 (a)
Male pseudohermaphrodite				ND			
Complete testicular feminization	1		28		1	0	0
Incomplete testicular feminization (b)	3	17.7 ± 4.2	13-21		2	1	0
Compartment 2							
Post chemotherapy	1		17	ND	1	0	0
Gonadal dysgenesis	33	22.5 ± 5.4	14-38		25	8	0
46,XX				150.5 ± 9.5			
45xXO and mosaic (c)				140.1 ± 5.1			
unknown karyotype (d)				143.0 ± 13.9			
Agonadism	1		18	154.0	0	1	0
Compartment 3				ND			
Hyperprolactinemia	1		27		1	0	0
Prolactinoma	1		28		0	1	0
Compartment 4							
Hypogonadotropic hypogonadism	8	21.4 ± 6.1	15-34	151.0 ± 9.7	6	2	0
Hypothalamic dysfunction (e)	5	22.8 ± 5.8	19-32	153.0	3	2	0
Others							
Congenital adrenal hyperplasia	1		25	ND	1	0	0
Primary hypothyroidism	2	19.0 ± 1.4	18-20	150.0	2	0	0
Total	101	22.5 ± 6.1	13-41		64	35	2

Note (a) Sexual problem 2 cases
(b) Clitoromegaly 3 cases
(c) Turner stigmata in all cases, Simple goiter 1 case, Hyperthyroidism and diabetes millitus 1 case, Aplastic anemia 1 case, Cataract 1 case, Osteoporosis 1 case.
(d) Turner stigmata 1 case, Simple goiter 1 case
(e) Obesity 1 case
S = single, M = married, D = divorced, ND = not done

Table 2. Findings of pelvic examination and ultrasonography of patients with Mullerian agenesis or hypogonadism.

Findings	Mullerian agenesis	Hypogonadism
Pelvic examination		
V+, Ut+	0	29
V+, Ut-	24	4 (a)
V-, Ut-	7	1 (b)
Ultrasonography		
Ut+, O+	0	1
Ut+, O-	0	2
Ut-, O-	0	2 (c)
Ut-, O+	9	0

Note (a) wrong diagnosis of absent uterus
(b) Embryonal testicular regression syndrome
(c) wrong diagnosis of absent uterus 1 case
Embryonal testicular regression syndrome 1 case
V = vagina, Ut = uterus, O = ovary, + = present, - = absent

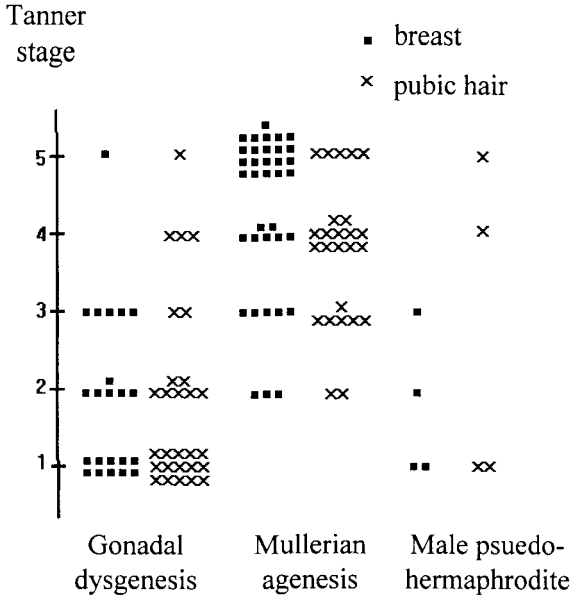

Fig. 1. Distribution of Tanner stage of the patients from compartment 2 (Gonadal dysgenesis) and compartment 1 (Mullerian agenesis and Male pseudohermaphrodite).

dite who had mosaic pattern (45,XO/46,XX/46, XY) (Table 3).

DISCUSSION

Primary amenorrhoea is a symptom of various diseases. It is accepted by standard textbook in Reproductive Endocrinology that the 3 most common diseases causing this symptom are gonadal dysgenesis, Mullerian agenesis and testicular feminization respectively[1]. Abnormal karyotypes are common in gonadal dysgenesis, i.e. 45,XO 50 per cent and mosaic 25 per cent[1], however, the incidence in varied[7-9].

We found the difference in our study. The 3 most common diseases were Mullerian agenesis, gonadal dysgenesis and hypogonadotropic hypogonadism respectively. Similar to our study, a study from India by Rao K and Pillai N[10] found that Mullerian agenesis was the most common cause of primary amenorrhoea. The similar findings from our neighbor country raised the hypothesis that racial and environmental differences may have a role in the causes of primary amenorrhoea. There was a report of familial mullerian anomalies which suggested that heritable aspects, either genetic or environmental factors, may be the causes[11].

Table 3. Cytogenetic study in primary amenorrhoea.

Diagnosis	No.	Karyotype			
		46,XX	46,XY	45,XO	Other
Compartment 1					
Mullerian agenesis	22	19	0	0	3 (a)
Male pseudohermaphrodite	4	0	3	0	1 (b)
Compartment 2					
Gonadal dysgenesis	28	14	2	4	9 (c)
Agonadism	1	0	1	0	0
Compartment 3					
Compartment 4					
Hypogonadotropic hypogonadism	5	5	0	0	0
Hypothalamic dysfunction	1	1	0	0	0
Others					
Congenital adrenal hyperplasia	1	1	0	0	0
Primary hypothyroidism	1	1	0	0	0

Note (a) 45,XO/46,XX
(b) 45,XO/46,XX/46,XY
(c) 45,XO/46,XX 6 cases
45,XO/46,XY 1 case
45,XO/46,XiXq 1 case
46,XiXq 1 case

Abnormal karyotypes were not common in our patients but with our method for karyotyping, we could not exclude the possibility of structural abnormality such as small chromosome fragment deletion and translocation. Besides, karyotyping from peripheral lymphocyte has limitation in diagnostic value for gonadal dysgenesis since abnormal karyotype may be found only in biopsied tissue from skin or gonadal streak[12]. Had we done such biopsies in gonadal dysgenesis with normal lymphocytic karyotype, we should have found a higher incidence of abnormal karyotype in this group. It is also important to identify fragment of Y chromosome (usually with Y-probe) in the patients[1]. If fragment of Y chromosome was found, the gonadal streaks have to be removed since they have a risk for gonadal neoplasm. In places where laboratory facilities for this technic are not available, like our institute, patient follow-up with meticulous clinical evaluation for signs and symptoms of gonadal tumor is still useful.

Problems of patients who have amenorrhoea include feeling of defeminization, fertility concern, sexual problems, problems related to hypoestrogenic stage and problems from the nature of the etiology with or without associated diseases. The latter two problems may not be known by the patients but they are certainly significant problems[2].

Feeling of defeminization due to an absence of menstruation and/or undeveloped secondary sexual characteristics seems like a minor problem for doctors. But for our patients, even though they were in late adolescence to adulthood, the majority of them were single and they were still unmarried even after being treated for years. The main reason was their belief that they were "not normal women". Careful counseling, especially to low educated patients, has to be introduced not only to inform them of the nature of their disease but also to confirm their femininity[1].

Fertility concern is the following problem. After definite treatment of some diseases such as hyperprolactinemia, hypothyroidism, the patients can get pregnant naturally[1,13] but the majority of primary amenorrhoea patients need some help. Various types of assisted reproductive technic are helpful for these patients, e.g. surrogate mother with the patient's oocytes for Mullerian agenesis, adoption of oocyte for gonadal dysgenesis[14] and ovulation induction with gonadotropins or gonadotropin releasing hormone for hypogonadotropic hypogonadism[2]. However, these technics are so expensive that only a few patients can afford them. Adoption is another choice to offer when counseling the patient.

Sexual problems were not one of the chief complaints in our patients but it may be a hidden problem and actually lead some patients to see us. Because of the Thai culture, it is not easy for a woman to talk or complain about sex. Thus, a doctor has to uncover this problem by always asking her but at the appropriate time. In our study, 4 patients of Mullerian agenesis had sexual problems and 2 of them divorced because of this problem. We should have found a higher incidence of this problem if we had asked not only the Mullerian agenesis but all patients.

Problems with hypoestrogenic stage, like menopause, such as early osteoporosis and cardiovascular diseases can be prevented or even improved with hormonal replacement therapy (HRT)[15]. In our series, there were more than 50 per cent of patients (compartment 2, 3 and some of 4) who had hypoestrogenic stage. They should have received early HRT in order to gain nearly normal maximal bone mass, as we know that the rate of bone mass deposition is high during adolescence and peaks around 25-30 years old[16,17]. Our patients received HRT rather late because the average age that they came to see the doctors were 22 $\pm$ 6 years when most of the gold period had gone. One of our patients, who was referred from an orthopedist when she first consulted him at 38 years old, had bone pain. Her plain film X-ray showed osteoporosis. Her final diagnosis was Turner syndrome. We do not know the actual incidence of osteoporosis in our patients because this problem has not been surveyed in our clinic yet.

Different diseases that cause primary amenorrhoea possess a different nature, i.e. different significant problems; mullerian agenesis patients may have anomalies in the urinary tract or vertebral spine[18]; gonadal dysgenesis patients, esp. Turner syndrome, may have multiple organ defects[19]; hypogonadotropic hypogonadism patients may have a brain tumor[1]; patients who possess chromosome y may be virilized or may have gonadal

neoplasia[20]. This is why we have to investigate the patients until final diagnosis can be concluded. It is important to pay attention to these problems in addition to those previously mentioned.

The laboratory investigations for primary amenorrhoea patients are not unique. It depends on the provisional diagnosis suggested by the clinical findings[21]. No investigation is the best one. Errors can be made by any test. They may come from the investigators, the instruments or the condition of the patients. Data from Table 2 shows one of these errors. The error of diagnosis of an absent uterus, actually the patients did have uterus, occurred in a case with a hypoplastic uterus due to severe hypoestrogenic stage. Thus, if there is something weird, we should reconsider all of the data.

In conclusion, the incidence of etiologic causes and cytogenetic study of primary amenorrhoea in our study are different from earlier reports. Racial and environmental differences may play a role in these differences. The improvement in diagnostic tools may also take part in the differences. However, clinical examination and many laboratory investigations have to be completed before final diagnosis of etiologic causes of primary amenorrhoea are elucidated. Diagnosis based on inadequate data can be misleading.

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ภาวะขาดระดูปฐมภูมิ: การศึกษาย้อนหลังที่โรงพยาบาลศิริราช

มณี รัตนไชยานนท์, พ.บ., สมบูรณ์ คุณาธิคม, พ.บ.*,*
สุรศักดิ์ อังสุวัฒนา, พ.บ., กิติรัตน์ เตชะไตรศักดิ์, พ.บ.*,*
อรวรรณ เมฆมหรรณพ์, พ.บ., จารุณี คารวะกุล, พ.บ.*, สมจิตร ก่ออนันตกูล, พ.บ.**

ได้ศึกษาอุบัติการของโรคที่เป็นสาเหตุของภาวะขาดระดูปฐมภูมิในโรงพยาบาลศิริราช โดยศึกษาจากแฟ้มประวัติของผู้ป่วยที่มารับการตรวจรักษา ณ คลินิกประจำเดือนผิดปกติ ที่ตึกผู้ป่วยนอกโรงพยาบาลศิริราช ระหว่างวันที่ 1 กันยายน 2535 และ 31 สิงหาคม 2538 พบว่าในระยะเวลาดังกล่าวมีผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะขาดระดูปฐมภูมิทั้งสิ้น 110 ราย ผู้ป่วยที่ถูกตัดออกจากการศึกษามีจำนวน 9 ราย เป็นผู้ป่วยที่ขาดการติดต่อไปก่อนที่จะได้รับการวินิจฉัยโรคที่แน่นอน จากผู้ป่วย 101 ราย พบว่าโรคที่เป็นสาเหตุที่พบมากที่สุด 2 อันดับแรก คือ mullerian agenesis (ร้อยละ 39.65) และ gonadal dysgenesis (ร้อยละ 32.69) อายุเฉลี่ยของผู้ป่วยเมื่อเริ่มมารับการรักษา คือ 22.45 $\pm$ 6.06 ปี ผลการตรวจโครโมโซมในผู้ป่วย gonadal dysgenesis จำนวน 28 ราย จาก 32 ราย พบว่าผู้ป่วยส่วนใหญ่มีโครโมโซมเป็น 46,XX (ร้อยละ 50) ส่วน 45,XO ตรวจพบเพียงร้อยละ 14.29 วิธีการตรวจต่าง ๆ เพื่อประเมินสภาพของมดลูกให้ข้อมูลที่ผิดพลาดได้ในผู้ป่วยที่มีมดลูกขนาดเล็กมากเนื่องจากการขาดฮอร์โมนเอสโตรเจน โดยพบความผิดพลาดจากการตรวจร่างกาย 4 ราย, จากการตรวจด้วยอัลตร้าซาวนด์ 1 รายและการตรวจโดยใช้กล้องส่องเข้าช่องท้อง 1 ราย ซึ่งผู้ป่วยทั้ง 4 รายนี้สามารถมีระดูได้ภายหลังการให้ฮอร์โมนเพศทดแทน ผลจากการศึกษานี้พบว่าอุบัติการของโรคที่เป็นสาเหตุและลักษณะโครโมโซมของผู้ป่วยแตกต่างจากรายงานอื่นเล็กน้อย ความแตกต่างนี้อาจเป็นผลจากความแตกต่างในเชื้อชาติและสภาพแวดล้อมรวมตลอดจนความสามารถของเครื่องมือที่ใช้ช่วยในการวินิจฉัย อย่างไรก็ดีผู้ป่วยทุกรายจะต้องได้รับการตรวจโดยละเอียดเพื่อได้รับการวินิจฉัยและการรักษาโรคที่ถูกต้อง

* ภาควิชาสูติศาสตร์นรีเวชวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700