



# National survey of primary amenorrhea and relevant conditions in Japan

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## Abstract

**Aim:** In Japan, most of the patients with primary amenorrhea or related conditions, such as delayed menarche, are diagnosed by pediatricians or gynecologists; accordingly, the number of the patients and the ratio of the causes were unclear. To clarify them, we conducted a nationwide survey in both the departments for the first time.

**Methods:** We sent a questionnaire about the patients with chief complaint of no menarche whose first visit was from January 2015 to December 2017, to 596 training institutions for specialist physicians of the Japan Society of Obstetrics and Gynecology and 152 facilities to which councilors of the Japanese Society for Pediatric Endocrinology belong.

**Results:** We received replies from 283 (37.8%) institutions. During the 3 years, 1043 patients first visited pediatrics or gynecology for no menarche. In 303 patients under 16 years old at the first visit, 177 (58.4%) patients had menarche by the age of 16. Of them, 41 (13.5%) patients had menarche spontaneously. Among 308 patients aged 16 to 17 at the first visit, 216 patients were 18 years or older at the survey. Of them, 124 (57.4%) patients had menarche by the age of 18, and 21 (9.7%) of them had menarche spontaneously. The causes of amenorrhea were detected in 462 patients. Abnormal karyotype including Turner syndrome was the most common at 122 (26.4%), followed by Mullerian agenesis at 73 (15.8%).

**Conclusions:** The first national survey revealed the number and causes of primary amenorrhea and related conditions. This report will provide better information for clinicians.

**Key words:** delayed menarche, national survey, primary amenorrhea.

## Introduction

Primary amenorrhea is defined as a condition in which a girl has not experienced menarche by 18 years of age in Japan. Various diseases and conditions may cause primary amenorrhea. It is important

for patients of primary amenorrhea to identify the cause. The main causes are anatomical defects and endocrine disorders.<sup>1</sup> In Japan, most of the patients are diagnosed by pediatricians or gynecologists. However, cooperation between pediatricians and gynecologists in this field are indigent, therefore proportion

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of the causes is unclear. In Japan, it is important that both doctors work together to provide early treatment.

In addition, a new term ‘delayed menarche’ was proposed recently by the Japan Society of Obstetrics and Gynecology (JSOG), that describes a condition in which a girl has never experienced menarche by 15–17 years of age.<sup>2</sup> The reason why this new term was introduced is to promote evaluation of ovarian status and intervention at the timing younger than 18 years old because of the pivotal role of pubertal estrogen for bone and emotional health, although the most appropriate age for the initial assessment of pubertal status is still controversial. However, it is totally unknown the number and prognosis of the patients who visited clinics with chief complaint of no menarche before the age of 18 years old.

In the present study, to uncover the current status of primary amenorrhea and relevant conditions in Japan, we investigated the patients with chief complaint of no menarche for pediatrics and gynecology.

## Materials and Methods

We sent questionnaires in July 2018 to 596 training institutions for specialist physicians of the Japan Society of Obstetrics and Gynecology, and 152 facilities to which councilors of the Japanese Society for Pediatric Endocrinology belong. The questionnaires were designed for patients with chief complaint of no menarche first visited from January 2015 to December 2017. The questionnaires were composed of three parts according to the patients’ age at the first visit; for the patients under 16 years old at the first visit and aged 16 years or older on December 31, 2017, for those aged 16 to 17 years old at the first visit, and for those aged 18 years or older at the first visit. For the first age group, it was asked whether the patients experienced menarche by the age of 16 and whether the menarche was spontaneous or medically induced. For the second group, among the patients who were 18 years or older on December 31, 2017, it was asked whether the patients experienced menarche by the age of 18 and whether the menarche was spontaneous or medically induced. The causes of amenorrhea were also asked. The study protocol was approved by the University of Tokyo’s review board (authorization reference number: 11967).

## Results

We received replies from 283 of 748 facilities (37.8%) in the survey. In 596 facilities of obstetrics and gynecology, we received replies from 223 facilities (37.4%). In 152 facilities of pediatrics, responses were obtained from 60 facilities (39.5%). The total number of patients first visited with chief complaint of no menarche during the 3 years was 1043, with 917 (87.9%) of them visited obstetrics and gynecology. Three hundred and three patients (29.1%) were under 16 years old, 308 (29.5%) were 16 to 17, and 432 (41.4%) were 18 years or older at the first visit. The proportion of the patients who visited pediatrics was getting lower when the age of the first visit increased; 24.8%, 9.4% and 5.1% in patients under 16, 16 to 17 and 18 or older, respectively.

As shown in Table 1, in 303 patients under 16 years old at the first visit, 177 (58.4%) patients had menarche by the age of 16. Of them, 41 (13.5%) patients had menarche spontaneously by the age of 16 without medical treatment. Among 308 patients aged 16 to 17 at the first visit, 216 patients were 18 years or older at the survey. Of them, 124 (57.4%) patients had menarche by the age of 18, and 21 (9.7%) of them had menarche spontaneously by the age of 18 without medical treatment (Table 1).

The causes of amenorrhea were detected in 462 patients (Table 2). When the causes were classified into four categories according to the affected sites, anatomic defects, primary hypogonadism, hypothalamic or pituitary causes, and other causes, primary hypogonadism was the leading cause, accounting for 39.2% of whole cohort, followed by anatomic defects (28.7%) and hypothalamic or

**Table 1** Prognosis of the patients under 18 years at first visit

<16 years at the first visit and ≥16 years at the survey ( <i>n</i> = 303)	
Menarche by the age of 16	177 (58.4%)
Spontaneously	41 (13.5%)
With medication	136 (44.9%)
No menarche at the age of 16	126 (41.6%)
16–17 years at the first visit and ≥18 years at the survey ( <i>n</i> = 216)	
Menarche by the age of 18	124 (57.4%)
Spontaneously	21 (9.7%)
With medication	103 (47.7%)
No menarche at the age of 18	92 (42.6%)

**Table 2** Causes of amenorrhea

	Total, <i>n</i> = 462	
Anatomic defects	128 (28.7%)	
Disorder of hymen or vagina (e.g., imperforate hymen, transverse vaginal septum)		25 (5.4%)
Mullerian agenesis (e.g., Mayer-Rokitansky-Kuster-Hauser syndrome)		73 (15.8%)
Defect in androgen action (e.g., CAIS, PAIS)		30 (6.5%)
Primary hypogonadism	181 (39.2%)	
Abnormal karyotype (e.g., Turner syndrome)		122 (26.4%)
Pure gonadal dysgenesis		29 (6.3%)
Enzymatic deficiency (e.g., 17-Hydroxylase deficiency, P450 oxidoreductase deficiency)		2 (0.4%)
Iatrogenic (e.g., chemotherapy, radiation)		28 (6.1%)
Hypothalamic or pituitary causes	123 (26.6%)	
Tumor		25 (5.4%)
Nutrition-related (e.g., eating disorders)		37 (8.0%)
Gonadotropin deficiency (e.g., Kallmann syndrome, idiopathic hypogonadotropic hypogonadism)		57 (12.3%)
Pituitary hormone deficiency (e.g., idiopathic pituitary hormone deficiency)		4 (0.9%)
Other causes	30 (6.5%)	
Polycystic ovary syndrome		25 (5.4%)
Prader-Willi syndrome		4 (0.9%)
VATER association		1 (0.2%)

Abbreviations: CAIS, complete androgen insensitivity syndrome; PAIS, partial androgen insensitivity syndrome.

pituitary causes (26.6%). Divided into the subcategories, abnormal karyotype including Turner syndrome was the leading cause, accounting for 26.4% of whole cohort, followed by Mullerian agenesis including Mayer-Rokitansky-Kuster-Hauser syndrome (15.8%) and gonadotropin deficiency including Kallmann syndrome and idiopathic hypogonadotropic hypogonadism (12.3%). Among other causes, it is noteworthy that nutrition-related causes including eating disorder accounts for 8.0%.

## Discussion

In Japan, patients with no menarche often visit pediatric or gynecological department, and no national survey was conducted through both departments. Therefore, the number of patients with primary amenorrhea and related conditions, such as delayed menarche, in Japan and the ratio of the causes were uncertain. Our study showed that approximately 350 patients per year first visit pediatrics and gynecology due to no menarche. As the age of patients increased, the percentage of gynecological consultations was getting higher than that of pediatrics.

In 303 patients less than 16 years old at first visit, 41.6% of them remained amenorrhea at the age of 16, and in 216 patients aged 16 to 17 at the first visit

and 18 years or older at the survey, 42.6% of them remained amenorrhea at the age of 18. These results indicate that clinicians tend to postpone hormonal therapy until 18 years of age, a virtually solid indication for estrogen replacement. However, only 13.5% of 303 patients under 16 years old at first visit had spontaneous menarche by the age of 16, and 9.7% of 216 patients aged 16 to 17 at first visit experienced spontaneous menarche by the age of 18. Taken together, given that the patients under 16 years old at first visit without spontaneous menarche by the age of 16 (86.5% of the cohort) would follow same natural course as the patients aged 16 to 17 at first visit (9.7% of them experienced spontaneous menarche by the age of 18), it is expected that only 21.9% (=13.5% + 86.5\*9.7%) of the girls under 16 years old who visit clinics with chief complaint of no menarche may have spontaneous menarche by the age of 18 years old. Patients with no menarche under the age of 18 may have spontaneous menarche by the age of 18. Therefore, the definition of primary amenorrhea in Japan seems reasonable. However, it is not advisable to observe them easily, and treatment and diagnosis at an early stage is important.<sup>1,3,4</sup>

As for the cause of amenorrhea, primary hypogonadism was the leading cause, accounting for approximately 40% of whole cohort, followed by anatomic defects and hypothalamic or pituitary causes

that account for 30%, respectively. The etiology in Japan seems almost the same as that in United States, although a very few published papers presented the etiology of primary amenorrhea with different definition of primary amenorrhea. Examination of 252 patients in United States revealed that gonadal dysgenesis accounted for 50%, hypothalamic or pituitary causes for 25% and anatomic defects for 20%.<sup>3,5</sup> Practice Committee of American Society for Reproductive Medicine showed in their review paper, referring a survey in 1982, summarized that primary hypogonadism accounted for 40%, hypothalamic or pituitary causes for 30% and anatomic defects for 30%.<sup>1,6</sup> Looking into the subcategories such as abnormal karyotype, Mullerian agenesis, gonadotropin deficiency and defect in androgen action, the etiology was almost the same as previous reports.<sup>1,3,5,6</sup> However, the proportion of nutrition-related causes was much higher in Japan than in United States (8.0% vs 3.0%<sup>1</sup>). The leanness is a big health problem in young women in our country these days and it is well known that body weight loss often causes secondary amenorrhea. The results of this survey suggest that a considerable number of girls before menarche were already affected by nutrition-related problems.

In this survey, we also asked the therapeutic strategy for patients with Turner syndrome that accounts roughly two thirds of gonadal dysgenesis, the leading cause of amenorrhea in both Japan and United States. The results gave us insight into transitional medical care for these patients. In our country, gynecologists did not conduct replacement of growth hormone (GH); pediatricians were responsible for GH therapy. Estrogen replacement therapy (ERT) was usually initiated around 12 years old, with body height of 140 cm. Patient care seemed to be transferred from pediatricians to gynecologists when ERT was replaced with hormone replacement therapy (HRT), around 15 years old.

There are some limitations in this study. One is that this survey targeted educational facilities. It is expected that most of the clinicians refer their patients without menarche to educational facilities in case that the patient is over 18, who meets diagnostic criteria of primary amenorrhea, or shows other health problems in addition to no menarche. However, it is conceivable

that a considerable number of patients under 18 and healthy expect for no menarche are followed-up by family physicians, who were not detected by this survey. Another limitation is that this survey did not collect the detailed medical intervention provided for each patient.

In conclusion, this is the first nationwide survey of primary amenorrhea and related conditions in Japan. This report will provide better information for Japanese clinicians and help them to provide appropriate medical service for patients with primary amenorrhea or those who may develop primary amenorrhea in future.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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