Bangladesh J Obstet Gynaecol, 2008; Vol. 23(2) : 46-50

Original Articles

Primary Amenorrhoea - Analysis of 44 cases

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Abstract

Objective: *To determine the etiologic factors responsible for primary amenorrhoea on the basis of clinical examination and laboratory investigations.*

Materials & Methods: *This retrospective study was done in a private setting from the records of the patients between January 2005 - December 2007.*

Results: *During three years of study period, 44 cases of primary amenorrhoea were analyzed. Two most common etiologic factors were mullerian agenesis (36.3%) and gonadal dysgenesis (29.5%). Range of average age of the patients when they first consulted the physician was 13-32 years. Karyotyping was done on 10 of13 cases of gonadal dysgenesis; 46, XX karyotype was found in 50% and 45, XO in 10% of analyzed cases. Clinical examination gave wrong diagnosis of absent uterus in two cases who were in the hypoestrogenic stage with hypoplastic uterus; ultrasonography gave the wrong diagnosis in one case in this study. These patients successfully menstruated after hormone replacement therapy.*

Conclusion: *The 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 for diagnostic tools may also play a part. Both clinical examinations 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.*

Introduction:

For majority of pubertal girls menstruation is a final result of series of events which results in sexual maturity. Maturation of hypothalamus through several years of late childhood begins a cascade of events which finally results in establishment of normal menstrual cycle and menstruation [1]. The cascade is an interdependent link between the hypothalamus, anterior pituitary, ovary and reproductive tract. Amenorrhoea will result when there is a break in one or more places in this chain.

Primary amenorrhoea is literally defined as absence of menstruation by the age of 14 in absence of secondary sexual characteristics and by age 16 in presence of normal secondary sexual characteristics[2]. Indeed amenorrhoea represents a symptom and is itself not a diagnosis. It is a common presenting feature of a variety of distinct disorders occurring in 1-3% of women in reproductive age group [3]. Untreated amenorrhoea is associated with significant long term morbidity, especially in young women who are the population at risk of amenorrhoea. Early recognition of the definite etiology and institution of the appropriate treatment will minimize late complications [4].

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 [5]. Apart from these the incidence of the disease that causes this problem may vary from area to area due to different racial group of patients. Since there are few large series on this topic from Asia, the present study was undertaken to determine the etiologic factors responsible for primary amenorrhoea on the basis of clinical examination and laboratory investigations.

Materials & Methods

A retrospective study was performed from the medical record of the patients (collected previously) in a private

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setting from January 2005- December 2007 and there were 44 patients who were diagnosed having primary amenorrhoea. The work up of primary amenorrhoea patients comprises of :

- History taking- including chief complaint, present history, past history and family history.
- Physical examination- including general examination and rectal and/or pelvic examination (PR/PV).In cases where PR/PV could not give clear information about pelvic organs, transabdominal pelvic ultrasonography was advised.
- Laboratory investigations were ordered for diagnosis of the causes. The laboratory investigations of each patient depends on the provisional diagnosis derived from history and physical examination.

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

Group-1 : End organ failure or outflow tract obstruction
Group-2 : Gonadal failure
Group-3 : Pituitary cause
Group-4 : Hypothalamic cause
Group-5 : Other causes

Karyotyping:

The karyotype was determined using peripheral leukocyte culture and G- banding technique [6–8] .

Results

The three most common etiologic factors of primary amenorrhoea were mullerian agenesis (36.3%), gonadal dysgenesis (29.5%) and hypogonadotropic hypogonadism (6.81%) respectively.

Table-I

Clinical features of patient with primary amenorrhoea

Causes	No.	Age range when first consulted (yr)	Height (cm)	Marital Status		
				S	M	D
Group-1						
Transverse vaginal septum	2	14-16	ND	2	0	0
Tuberculous endometritis	1	30	ND	0	1	0
Mullerian agenesis	16	14-24	152±5	11	4(a)	1(a)
Male pseudo hermaphrodite -Complete testicular fertilization	1	13	ND	1	0	0
Group -2						
Post chemotherapy	1	17	ND	1	0	0
Gonadal dysgenesis	13	16-32		9	4	0
46XX			150±6			
45XO & mosaic (b)			140±5.1			
Agonadism	1	18	ND	0	1	0
Group -3						
Hyperprolactinemia	1	17	ND	1	0	0
Prolactinoma	1	16	ND	0	1	0
Group -4						
Hypogonadotropic hypogonadism	3	14-20	151±4	2	1	0
Hypothalamic dysfunction (c)	1	15	153	0	1	0
Others						
Primary hypothyroidism	1	18	150	1	0	0
Congenital adrenal hyperplasia	1	22	ND	1	0	0
Androgen secreting tumour	1	14	ND	1	0	0
Total	44	13-32		30	13	1

Note: (a) Sexual problems in two cases.
(b) Turner stigma in all cases, simple goiter in one case, hyperthyroidism and diabetes one case, osteoporosis one case.
(c) Obesity in one case.
S=single, M=married, D=divorced, ND=not done.

Clinical feature of the patients are shown on table-I. The age range of the patients when they first consulted the physician was 13-32 years. The oldest patient was a case of gonadal dysgenesis (32years) whereas the youngest was male pseudo hermaphrodite (13years). The majority of the patients were single. There were two cases of mullerian agenesis having sexual problems which lead to divorce in one case. The height of the patients were not clinically different among the five groups while patients having Turner syndrome was still the shortest.

The development of secondary sexual characteristics were more advanced in the group-1 defect than the group-2 defect.

Pelvic examination gave wrong diagnosis of absent uterus in two cases who were in the hypoestrogenic stage with hypoplastic uterus; ultrasonography gave wrong diagnosis in 1 case. These patients successfully menstruated after hormonal replacement therapy (table-II).

Karyotyping was done on 10 of 13 cases of gonadal dysgenesis. 46, XX karyotype was found in 5 patients (50%), mosaic in 3 patients (30%) and 45 XO in 1 patient (10%). Others possessed normal karyotype (either 46, XX or 46XY) except a case of male pseudo hermaphrodite who had mosaic pattern (45, XO/46, XX/46, XY) (table-III).

Table-II

Finding of pelvic examination and ultrasonography of patients with mullerian agenesis or hypogonadism.

Finding	Mullerian Agenesis	Hypogonadism
Pelvic examination		
Vagina present, uterus present	0	10
Vagina present, uterus absent	10	2
Vagina absent, uterus absent	3	0
Ultrasonography	0	
Uterus present, ovary present	0	1
Uterus present, ovary absent	0	2
Uterus absent, ovary absent	3	1
Uterus absent, ovary present		0

Table-III

Cytogenetic study in primary amenorrhoea

		46,XX	46,XY	45,XO	Others
Group-1					
Mullerian agenesis	16	16	0	0	0
Male pseudo hermaphrodite	1	0	0	0	1(a)
Group-2					
Gonadal dysgenesis	10	5	1	1	3(b)
Group-3					
Group-4					
Hypogonadotropic hypogonadism	3	3	0	0	0
Hypothalamic dysfunction	1	1	0	0	0

Note: (a) 45, xo/ 46, xx/ 46, xy

(b) 45, xo / 46, xx^{-2}

45, xo / 46, xy^{-1}

Discussion:

Primary amenorrhoea is a symptom of different diseases. It is accepted by standard textbook in Reproductive Endocrinology that the three most common diseases causing this symptom are gonadal dysgenesis, mullerian agenesis and testicular feminization respectively [9]. Abnormal karyotype are common in gonadal dysgenesis, i.e. 45, XO 50% and mosaic 25%, however the incidence in varied [10–12].

In this study, the three most common causes of primary amenorrhoea were mullerian agenesis, gonadal dysgenesis, hypogonadotropic hypogonadism respectively. Similar to this study, a study from India by Rao K and Pillai N [13] and a study from Thailand by Rattanachaiyanont [14] found that mullerian agenesis is the most common cause of primary amenorrhoea. Similar finding from neighboring country raised the probability that racial and environmental differences may have a role in causing primary amenorrhoea.

Abnormal karyotypes were not common in our patients and with our method for karyotytping, we could not exclude the possibility of minor structural abnormality such as small chromosome fragment deletion and translocation. Besides, karyotytping from peripheral lymphocyte has limited diagnostic value for gonadal dysgenesis since abnormal karyotype may be found only in biopsied tissue from skin or gonadal streak[15].

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 etiology with or without associated diseases. The latter two problems may not be known by the patients but they are certainly significant problems [4].

Feeling of defeminization due to 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 the 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 [9].

Fertility concern is the next problem. After definite treatment of some diseases such as hyperprolactinemia, hypothyroidism, the patients can get pregnant naturally[9,16] but the majority of primary amenorrhoea patients need some help. Various types of assisted reproductive techniques are helpful for these patients, e.g. surrogate mother with patient's oocytes for mullerian agenesis[17] and ovulation induction with gonadotropins, or gonadotropin releasing hormone for hypogonadotropic hypogonadism [4]. However these techniques are so expensive that only a few patients can afford them.

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

Problems with hypoestrogenic stage, such as early osteoporosis and cardiovascular diseases can be prevented or even improved with hormonal replacement therapy (HRT)[18]. In our series there were more than 50% patients (group 2,3and some of 4) were in hypoestrogenic stage. They should have received early HRT in order to gain nearly normal bone mass, as we know that the rate of bone mass deposition is high during adolescence and peaks around 25-30 years[19,20]. Our patients received HRT rather late because the average age at which they came to see the physician was 22±3 years.

Different diseases that cause primary amenorrhoea can produce other significant problems; mullerian agenesis patients may have anomalies in urinary tract or vertebral spine[21]; gonadal dysgenesis patients, especially Turner syndrome, may have multiple organ defect[22]; hypogonadotropic hypogonadism patients may have a brain tumor [9]; patients who possess chromosome Y may be virilized or may have gonadal neoplasia[23]. This is why we have to investigate the patients until final diagnosis can be reached. It is important to pay attention to these problems in addition to those previously mentioned.

In conclusion, 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 improvement of diagnostic tools may also make these differences. 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.

References:

1. Neerja Bhatla. Amenorrhoea, hypomenorrhoea & oligomenorrhoea, Jeffcoate's Principles of Gynaecology, International Edition (6th) 2001, Page-541.
2. Donelle Laugh Lin and Ian H. Thorneycroft. Amenorrhoea; Current- Obstetric and gynecologic diagnosis and treatment, 9th Edition-2002, page- 991.
3. S.S. Ratnam and R. Jothi Kumar. Amenorrhoea, Obstetric and gynecology for post graduate. 2nd Edition-1999; Vol.-1, Page- 241.
4. Schachter M, Shoham Z. Amenorrhoea. During the reproductive years - is it safe? Fertil Steril. 1994, 62: 1-16.
5. Kallio H. Cytogenetic clinical study on 100 cases of primary amenorrhoea. Acta Obset Gynecol Scand Suppl 1973; 24 (Suppl): 1-78
6. Moorhead PS, Nowell PC, Mellman WJ Battips DM Hungerford DA. Chromosome preparations of leucucytes cultured from human peripheral blood. EXP cell Res 1960; 20: 613-6.
7. Seabright M. A rapid banding technique for human chromosomes. Lancet 1971; 2: 971-2.
8. Seabright M. Human chromosome banding. Lancet 1972; 1: 967.
9. Speroff L, Glass RH, Kase N. Amenorrhoea. In Speroff L, Glass RH, Kase N. eds. Clinical gynecologic endocrinology and fertility. 5th edition. Baltimore: Williams and Wilkins, 1994: 401-56.
10. Aimakhu Ve, Akinkunmi SA. Cytogenetic studies in primary amenorrhoea. Acta Cytologica 1975; 19: 342-4.
11. Kosanovic M, Nikolis J, Diklik Vet al. Infrequent structural chromosome aberrations in women with primary amenorrhoea. Int JFertil 1979; 24: 68-70.
12. Khoo SK Mackay EV. Primary amenorrhoea: A study based on clinical examination, chromosomal analysis, eddocrine assay and laparoscopy. Med J Australia, 1972; 2: 1991-6
13. Rao K, Pillii N V. Primary amenorrhoea (analysis of 40 cases). J Indian Medical Association 1991; 89: 42-3.
14. Rattanachaiyanont and Kunathikom Primary amenorrhoea: a retrospective study at Siriraj Hospital: J Med Assoc Thai 1997; 80 :619-25.
15. Surico N, Messina M, Ponzio G, et al. Limited diagnostic values of lymphocytic karyotype in primary amenorrhoea with streak gonads. Eur J Obset Gynecol Reprod Biol 1987; 26: 145-50.
16. Howlett TA, Wass JAH, Grossman A, Plowman PN, Charlesworth M, Touzel R, Prolactinomas presenting as primary amenorrhoea and delayed or arrested puberty: response to medical treatment. Clin Endicrinol (oxf) 1989; 30: 131-40
17. Devroey P, Wisanto a, Camus M, et al. Oocyte donation in patients without ovarian function. Hum Reprod 1988; 3: 699-704.
18. Munk- Jensen N, Pros Nielsen S, Obel EB , Bonne Eriksen P. Reversal of postmenopausal vertebral bone loss by estrogen and progestogen; a double blind placebo controlled study. Br Med J 1988; 296: 1150-2.
19. Ott SM. Attainment peak bone mass J Clin Endocrinol Metab 1990; 71: 1082 a-c.
20. White CM, Hargenroeder AC, Klish WJ, Bone mineral density in 15-21 year old eumenorrheic and amenorrheic subjects. Am J Dis Child 1992; 146: 31-5
21. Mahajan P, Kher A, Khungar A, Vhat M, Sank Lecha M, Bharucha BA. MURCS association- a review of 7 cases, J Postgrad Med 1992; 38:109-11,
22. Rosenfeld RG, Tesch LG, Rodriguez-Rigau LJ, et al. Recommendation for diagnosis, treatment, and management of individuals with Turner syndrome. Endocrinologist 1994; 4: 351-8,
23. Anuman-Rajdhon Y, Suvatte A. Development of Germ cell Tumor in 46, XY Gonadal Dysgenesis: A report of two cases. J Made Assoc Thai 1983; 6: 82-7.