

AMENORRHOEA

Aetiological analysis

by

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and

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The term "amenorrhoea" denotes the absence or cessation of uterine bleeding and defines a clinical symptom rather than a clinical diagnosis. It forms one of the major problems in gynaecological practice and is a symptom complex which reflects some derangement in the hypothalamus-pituitary - ovarian - uterine axis. It is a symptom of a large number of diverse clinical entities, varying from organic brain diseases to local pelvic disorders. Detailed and exhaustive investigations are often required to ascertain the basic pathology and even then, no etiological factor may be found in a number of cases. However, an attempt has to be made to find out the underlying cause so that effective treatment can be given to the patient without further delay.

The cases of amenorrhoea are broadly classified as primary and secondary (Sutherland, 1956; Novak, 1961; Israel, 1963). Further classification of the primary and secondary amenorrhoea is done depending upon the etiological factors concerned.

Material and methods

An aetiological analysis of 102 cases of amenorrhoea seen at the gynaecological out-patients' department of the Lady Hardinge Hospital was made. Cases of physiological amenorrhoea, cryptomenorrhoea and of amenorrhoea secondary to general, systemic or such endocrine disorders as thyrotoxicosis or Cushing's syndrome were excluded from this study. The main emphasis is on gynaecological conditions. Out of 102 cases, 39 were of primary amenorrhoea and 63 of secondary amenorrhoea. The average age of menarche in India is between 13-14 years (Purandare, 1945; and Isreal, 1959). Those patients who had completed 17 years, but had not started menstruation, were considered as cases of primary amenorrhoea in this study.

The minimum duration of cessation of period after the last normal menstrual period to be considered as secondary amenorrhoea varies with different authors. Manzer Benaron (1962) considered it as an interval of at least 8 weeks in between periods, while Jones and Nalley (1959), Sutherland (1956) and Deshpande *et al* (1965) applied the term to a duration of 3 months or

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Received for publication on 27-9-1968.

more in between periods. The latter criteria have been used in this study.

Besides taking a detailed history and making a careful general and systemic examination, a pelvic examination was made under general anaesthesia and the uterine index was measured when considered necessary. A special note was made of the general body build, height, weight, span and development of secondary sex characters. Further special investigations were made depending on the suspected aetiological factors. These investigations were:

the internal genitalia was performed on two cases.

Observations

Primary Amenorrhoea

Secondary Sex Characters

From Table I, it is evident that the majority of cases with primary amenorrhoea had well developed secondary sex characters. The small discrepancy between breasts development (76.9%) and development of the external genitalia (82.05%) was probably due to the difference in response of each tissue to the ovarian hormones.

TABLE I
Showing development of secondary sex characters

Not developed	Breasts under developed	Well developed	External genitalia under developed	Normally developed	Inguinal testes
4	5	30 (76.9%)	7	32 (82.05%)	1

1. Buccal smear for sex chromatin.
2. Vaginal cytology to assess the hormonal status of the body.
3. Endometrial biopsy to assess the hormonal status of the body and to exclude tuberculosis.
4. 17-ketosteroid estimation in the urine.
5. Basal metabolic rate and blood cholesterol.
6. X-ray examination of the chest and skull.
7. Intravenous pyelography to exclude abnormality of the urinary tract.

Facilities to estimate gonadotrophic hormones were not available, and hence these were not estimated in any of the cases under study. Laparotomy to assess the status of

Development of Internal Genitalia

In contrast to well developed secondary sex characters, Table II shows that the internal genitalia were

TABLE II
Showing development of the internal genitalia

Normal	9	} 30(76.9%)
Hypoplastic	10	
Infantile uterus	3	
Absent uterus	17	

either hypoplastic or absent in most of these cases (76.9%). This undoubtedly is due to the fact that development of internal genitalia does not wholly depend upon the factors that are responsible for development of secondary sex characters. A certain amount of inherent development is necessary before ovarian

hormones can act on them. The major cause of primary amenorrhoea in the present series was under or non-development of the Müllerian ducts. One of the cases with well-developed external genitalia and absent uterus had inguinal testes (Table I), and was later found to be a case of testicular feminization.

The cases included in this study were between 18-30 years of age, 36 out of 39 cases being below the age of 24 years.

Hormonal status

Table III shows the results of vaginal cytology in 24 cases. It is seen

TABLE III
Vaginal cytology in 24 cases

Type of vaginal smear	No. of cases
Good oestrogen effect	13
Slight oestrogen deficiency	6
Moderate oestrogen deficiency	2
Marked oestrogen deficiency	2
Smear showing evidence of ovulation	1

that the majority of patients possessed adequate ovarian tissue. This confirmed the physical findings given in Table I. The case showing evidence of ovulation was a case of tubercular endometritis. No endometrium could be obtained in this case at curettage due to complete atrophy of the endometrium.

Sex chromatin

Sex chromatin studies were made in all 39 cases. Four (10.2%) were found to be chromatin negative. One of these cases was clinically found to be a case of ovarian agenesis (Turner's syndrome), and the other was that of testicular feminisation.

Urinary tract abnormalities

Since the genital and urinary tracts develop from the urogenital folds, developmental error of one system may reflect on the development of the other. Therefore, to detect abnormalities in the urinary tract an intravenous pyelography was done in 15 cases with genital tract abnormalities. Urinary tract abnormalities were present in 3 cases (20%). All these cases had solitary kidney, two in the normal position and one in the pelvis.

One case of primary amenorrhoea started menstruation at the age of 24 years while undergoing investigations.

Tubercular endometritis

As late as 1955, primary amenorrhoea was considered a rare manifestation of genital tract tuberculosis (Barnes 1955), though Oastler and Sutherland (1956) included it in their classification and an occasional case was reported by Reiss (1958). In the present study, dilatation and curettage or endometrial biopsy was performed in 16 cases, 9 having normal uteri and 7 having hypoplastic uteri. Histopathology report of one of these cases was tubercular endometritis, while no endometrium could be obtained in 11 cases (61.2%). This latter group was treated with cyclic oestrogen therapy for a period varying from 3 to 4 weeks and the endometrial biopsy was repeated. The histopathology report was positive for tuberculosis in 5 of these 11 cases, thus the total number of cases of proved tubercular endometritis was 6. In two cases, no endometrium could be obtained in spite

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of repeated courses of hormonal therapy followed by dilatation and curettage; these patients had normal physical development and were, therefore, considered as cases of endometrial tuberculosis having complete atrophy of the endometrium. Thus, there were 8 cases of tubercular endometritis out of 39 cases of primary amenorrhoea (20.5%). On excluding 30 cases of under or non-development of the

tween 4 months to 7 years, about 50% of them having been treated for it previously and the other 50% had not bothered to seek advice until 1-7 years had passed since the onset of amenorrhoea.

Significant past history

Significant past history was available in 23 patients. Table V gives some indication of the underlying pathology.

TABLE IV
Duration of secondary amenorrhoea

Period of amenorrhoea	3-11 months	1 year-3 yrs.	4 yrs.-6 yrs.	7 yrs.	Total
No. of Patients	34	19	9	1	63

TABLE V
Significant past history

Definite history of tuberculosis	Contact with tuberculosis	Post-partum haemorrhage	Dilatation & curettage	Abdominal operation	Intra-cranial trauma	Psychological stress	Total
6	5	2	2	1	1	6	23 (36%)

internal genitalia responsible for primary amenorrhoea, evidence of tubercular endometritis was found in 8 (89%) out of 9 normal cases.

Secondary amenorrhoea

Age in 63 patients of secondary amenorrhoea varied between 16-40 years. The maximum number of cases were between the age of 20-29 years, and the number of cases decreased as the age advanced.

Age at menarche

There did not appear to be any relationship between the age at menarche and secondary amenorrhoea as 56 patients out of 63 had attained menarche before the age of 18 years.

Duration of amenorrhoea

Table IV shows that the period of secondary amenorrhoea varied be-

Histopathology of the endometrium

Endometrial biopsy or dilatation and curettage was done in 50 cases. The type of endometrium obtained is shown in Table VI. It is seen that

TABLE VI
Histopathology of endometrium

No endometrium obtained	18 cases
Proliferative endometrium	11 cases
Proliferative endometrium with cystic dilation of glands	1 case
Secretory endometrium	7 cases
Tubercular endometrium	7 cases
Atrophic endometrium	5 cases
Chronic endometritis	1 case.

in 18 out of 50 cases, no endometrium could be obtained. In 10 of these 18 patients there was evidence of pulmonary tuberculosis and tubercular lymphadenitis. Four of these 10 patients started menstruating following anti-tubercular treatment. Tubercular endometritis

in 7 cases gave clear evidence of genital tuberculosis. Thus, 17 patients suffered from tuberculosis.

Three other cases of interest were between the ages of 30 and 40 years, they had attained premature menopause, the endometrium was found to be atrophic and vaginal cytology showed hormonal deficiency. They responded to hormone therapy.

Hypothyroidism was found in 3 cases; 2 of these started regular menstrual cycles following thyroid therapy. Anaemia (Hb. 5 gm%) was responsible for secondary amenorrhoea in one case. This patient responded to anti-anaemic treatment.

In one case amenorrhoea had followed head injury and in another case the ovaries had been removed during an abdominal operation. Obesity was responsible for secondary amenorrhoea in 3 cases in whom normal menstrual pattern followed reduction in weight.

In three patients with a history of pelvic inflammation, no endometrium was obtained and the uterine cavities were found fibrosed, probably due to destruction caused by a non-specific type of infection. One of these cases developed haematometra after oestrogen therapy, which was caused by cervical stenosis following local sepsis.

In 13 patients (20.6%) no cause could be found for the secondary amenorrhoea.

Discussion

The present study emphasizes the necessity of detailed investigations in every case of amenorrhoea, whether primary or secondary, to detect the underlying aetiological factor where-

ever possible, thus preventing the harm that can be done to the patients when attempts are made to produce withdrawal bleeding by hormones without a proper diagnosis.

Menarche may be delayed to a later age; it occurred at the age of 24 years in one of our cases. Shah (1961) found late maturity in 2 of his cases.

Negative sex chromatin patterns can explain some of the cases of primary amenorrhoea in whom delayed menarche and organic disease have been excluded. Kunwar *et al* (1966) found buccal smears showing negative chromatin pattern in 2 out of 23 cases (8.7%). Jacob *et al* (1959) showed the importance of sex chromatin study in cases of testicular feminization and Turner's syndrome. In the present study, 4 (10.2%) out of 39 cases of primary amenorrhoea had a negative sex chromatin pattern. On further investigations, one of these 4 cases was found to be a case of testicular feminization and another of gonadal dysgenesis.

The detection of urinary tract abnormalities in 3 out of 15 cases of primary amenorrhoea, particularly in those with genital tract abnormalities, shows the importance of doing intravenous pyelography specially in those cases where plastic repair of the genital tract is to be undertaken.

In the present series, tuberculosis was found to be responsible for primary amenorrhoea in 89% of cases which is a much higher figure than 33.3% reported by Asolkar. Prevalance of tuberculosis in our country, therefore, justifies an endometrial biopsy or dilatation and curettage even in unmarried girls

with primary amenorrhoea, particularly where the secondary sex characters are well developed and there is nothing to suggest hypofunction. Failure to carry out this procedure involves the risk of missing some cases of tubercular endometritis. Most of these cases were being treated with hormonal therapy but had failed to respond. This proves that the practice of initiating hormone therapy to promote sexual development and menstruation is to be deplored unless adequate diagnostic studies have been undertaken.

Relevant past history does help in some cases in revealing the etiological pathology. Of the 63 patients with secondary amenorrhoea, a significant past history was present in 23 (36%) cases.

In two cases of amenorrhoea following post-partum haemorrhage, there was no other evidence of Sheehan's syndrome, although vaginal cytology revealed some degree of ovarian hypofunction. This may be due to the fact that these two patients had a comparatively short history and the time interval was not long enough to give the full blown picture of the syndrome.

Amenorrhoea had followed dilatation and curettage in 2 cases. No endometrium was obtained on repeat curettage even after the administration of hormone therapy. In these cases the basal layer of the endometrium had been most probably removed by the previous vigorous curettage.

It is interesting to note that 6 patients suffered from psychological stress, and one of them, who had amenorrhoea of 2 years duration, started menstruating while she was

being investigated. This shows the importance of taking a detailed history, including psychological background of patients with secondary amenorrhoea.

History of tuberculosis or contact with such patients was obtained in 11 cases. The total number of patients with tubercular infection which was responsible for secondary amenorrhoea was 17 (27%). This incidence is higher than that reported by Asolkar (13.1%).

Conclusions

1. Genital tract abnormalities and tuberculosis seem to be the main causes of primary amenorrhoea.
2. Tuberculosis was the commonest cause of primary amenorrhoea in normally developed females.
3. The incidence of tuberculosis is higher in patients with primary amenorrhoea than in those with secondary amenorrhoea in whom various other acquired factors related to labour or otherwise seem to play a part.
4. A detailed past history is of great help in detecting the aetiology of amenorrhoea.
5. Dilatation and curettage in patients in whom no obvious cause of amenorrhoea is found, should be performed before starting any specific line of treatment.

Summary

1. Aetiological analysis of 102 cases of amenorrhoea seen at the outpatients' department of the Lady Hardinge Hospital was made. Out of these, 39 were of primary amenorrhoea and 63 of secondary amenorrhoea.

2. Out of 39 cases with primary amenorrhoea, 76.9% had underdeveloped internal genitalia in contrast to the normally developed external genitalia in most of these cases (82.05%).

3. Sex chromatin studies revealed 4 (10.2%) cases to be chromatin negative. One of these was a case of Turner's syndrome and the other one was that of testicular feminisation.

4. Urinary tract abnormalities were present in 20% of the cases with genital tract abnormalities.

5. Tubercular endometritis was found in 89% of cases of primary amenorrhoea after excluding genital abnormalities.

6. Tuberculosis was responsible for secondary amenorrhoea in 17 cases (27%).

7. Sheehan's syndrome, hypothyroidism, anaemia, obesity, pelvic infection and psychological factors were other causes of secondary amenorrhoea.

8. A plea is made for a detailed history including psychological background of the patient.

9. Initiation of hormone therapy to promote sexual development and menstruation, before adequate diagnostic studies have been undertaken, is condemned.

Acknowledgement

We wish to thank Dr. M. Chaudhuri, the Principal and Medical Superintendent, Lady Hardinge Medical College & Hospital, for allowing us to publish these data.

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