SOME OBSERVATIONS ON THE ETIOLOGY OF PRIMARY AMENORRHOEA—ANALYSIS OF 44 CASES

by

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Though the literature is replete with papers on various aspects of secondary amenorrhoea, few critical studies so far have been reported in the literature, both foreign and Indian, on not infrequently seen situations like delayed menarche and primary amenorrhoea. Careful definition of these two terms is advocated by several authors since delayed menarche could be physiological and therefore essentially a pubertal manifestation limited to two or at the most three years. Primary amenorrhoea on the other hand is considered a pathological condition and necessarily invades the adult or postpubertal period.

Failure of the onset of menstruation by completion of 16-17 years in this country should be considered as delayed menarche, and its continued absence after the completion of 17 years as primary amenorrhoea, since the average age of menarche in Indian subjects according to several authors is close to 13.5 years (Curjel, 1920; Israel, 1959; Parvatidevi, 1955; Purandare, 1945; Shah, unpublished data). The purpose of this communication is to show that these criteria are unnecessary and artificial especially when pathology is involved. We, however, feel that both these situations, viz. delayed menarche or primary amenorrhoea, should be taken little more seriously and a search should be made to find out the etiology prior to assuring the anxious mother that her daughter will eventually 'outgrow' the condition or before a prescription is enthusiastically scribbled down for some sort of withdrawal bleeding.

Method and Material. The clinical material comprised of 44 consecutive cases referred to the Endocrine Clinic at the Indian Cancer Research Centre by both gynaecologists and general practitioners. The main reason for their referring these patients to us was lack of facilities for special investigations. The patients belonged to the age span of 16-35 years.

Depending upon the sexual development and secondary sex characteristics, they were classified into 4 groups. The first group of "Sexual Infantilism" included patients who had no sexual development and absence of secondary sex characteristics. The second group of "Sexual Hypoplasia" constituted patients who were certainly not cases of sexual infantilism and yet were more than cases merely showing a hypoplastic uterus. The third group classified as "Normal Sexual Development" re-

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presents the best developed of these three groups, all having normal or nearly normal feminine figure except absence of menarche. The fourth group included cases who had abnormal sexual development.

A detailed medical history, a thorough physical examination and general laboratory tests of blood, urine and stool formed the basic framework before special investigations were thought of. Such an attitude appears to help maximally in excluding local abnormality or systemic diseases.

Special investigations like determination of genetic sex from buccal mucosal cells were carried out in each case. Serial vaginal smears, taken at an interval of 3-4 days, for about 3-4 weeks, were studied in most of the cases. Papanicolaou's schedule was followed for the preparation and staining of the smears. Endometrial tissue was histologically examined in as many cases as possible. Biochemical investigations, like measurement of urinary gonadotrophins, 17-ketosteroids or corticosteroids from a 24-hour sample of urine or radiographic studies of sella turcica or for bone age determination, were carried out whenever indicated.

Observations. Table I shows the frequency distribution of 4 clinical groups arranged according to the two conventional age groups. It is evident that the largest single group of 20 patients has normal sexual development and that 11 of 44 cases fall between the age range of so-called delayed menarche.

Table I

	CLINICAL GROUPS	DELAYED MENARCHE (16–17 years)	PRIMARY AMENORRHOEA (>17 years)	
I	SEXUAL INFANTILISM	4	7	11
II	SEXUAL HYPOPLASIA	2	7	9
III	NORMAL SEXUAL DEVELOPMENT	3	17	20
IV	ABNORMAL SEXUAL DEVELOPMENT	2	2	4
	TOTAL	11	33	44

The etiological factors involved in these patients are shown in Table II. It is clear from the table that etiologically there are no differences between these two age groups. The causative factors are varied and are commonly concerned with one of the three functional levels, viz. (i) anterior-pituitary or hypothalamus, (ii) gonad, and (iii) the peripheral level concerning uterus or vagina. In some cases, however, more than one interlocking etiological factors concerning pituitary-ovary-uterus were involved. In one case absence of menarche was due to the altered function of adrenal cortex producing excessive amount of androgens.

Before coming to these functional levels proper, we would briefly comment on the other etiological factors found in our series of cases. For example we had two cases of late maturity who without any treatment started menstruating within about 8 weeks after completion of the investigations and before any treatment was prescribed. Both these cases revealed normal functioning pituitary-ovarian-uterine axis. Evidently in these cases, it was the question of time before they could attain physiological maturity to initiate menstruation. Some of you may therefore object to pelvic examination or endometrial biopsy in such young, unmarried girls. We, however, feel such cases should always be examined and carefully investigated

because it is only rarely that we meet a happy situation like delayed maturity. Absence of menarche, especially in the group of "Normal Sexual Development", is more often than not due to congenital defects of uterus and/or vagina or to the destruction of the endometrium by tuberculous infection (Table V).

Under genetic defect, we have only one case who deserves special mention. This patient closely resembled the "Webb-Neck Syndrome" of Turner but, instead of absence of gonads, she had all the evidences of the presence of normal functioning gonads—normal secondary sex characteristics, good oestrogenic effect as seen by the changes in vaginal cytology and unelevated urinary gonadotrophins. The presence of rudimentary uterus was most probably responsible for absence of menarche in this case (Figs. 1 and 2). Rudimentary uterus, like stunted growth and other congenital anomalies accompanying this syndrome, could be due to genetic defect.

Coming to the nutritional factors, it is common knowledge that improperly balanced or insufficient diet affect the pituitary function adversely. Seven of our 44 cases had primarily nutritional deficiency—they were underweight, had short stature with normal body proportions, marked pallor of the skin and mucous membranes, absence of secondary sex characters and absence of demonstrable levels of urinary gonadotro-

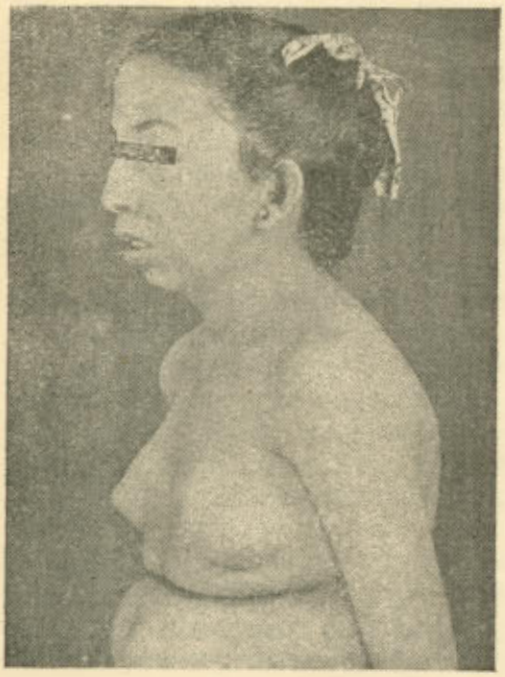

Fig. 1.

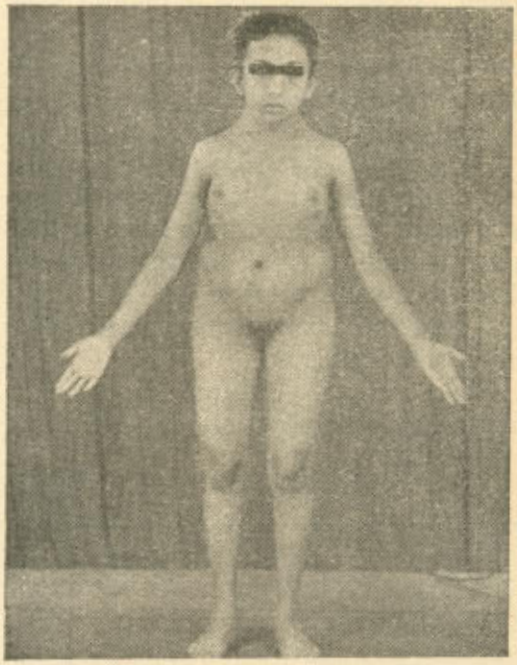

Fig. 2.

Fig. 1, 2—The "Webb-Neck" Syndrome (aged 17 years) but has all the evidences of normal functioning ovary-good development of breast, labia minora well pigmented, vagina oestrogenised, urinary gonadotrophins not elevated. The genetic sex of this case was female.

phins on repeated examinations. All these cases were treated for a considerable period of time with vitamins, proteins and haematinics without any beneficial results as far as the initiation of menstruation was concerned. On single or repeated stool examinations, 4 of these had Giardia lamblia infection and 3 had infection with Ascaria lumbricoides. Adequate deworming along with proteins, etc. improved the general health remarkably but menarche appeared in only 2 of these 7 cases. The uterus was found to be rudimentary in the remaining 5 cases long after successful therapy.

Now, coming to the three functional levels, we had 8 more cases in whom repeated estimations revealed absence of demonstrable level of urinary gonadotrophins. All these 15 cases are therefore classified under hypogonadotrophism (Table II).

Table II

ETIOLOGY	DELAYED MENARCHE (11)	PRIMARY AMENORRHOEA (33)	TOTAL
PHYSIOLOGICAL (Late maturity)	1	1	2
GENETIC	1	–	1
NUTRITIONAL	3	4	7 } 15
PITUITARY OR HYPOTHALAMUS	.....	.....	8 }
I) Infantilism & short stature		2	
II) Eunuchoidism		6	
OVARIAN EUNUCHOIDISM Congenital aplasia, Gonadal dysgenesis	1	1	2
UTERUS – VAGINA	.....	.....	23
I) Congenital absence of uterus and / or vagina	3	8	
II) Destruction of the Endometrium	1	10	
III) Insensitive Endometrium ?	–	1	
CONGENITAL ADRENAL VIRILISM.	1	–	1

The causative factors in these cases of hypogonadotrophism are shown in Table III. It is interesting to note that none of these cases had any of the known causes of hypogonadotrophism, viz. haemorrhage infection or tumour, e.g. chromophobe adenoma or craniopharyngioma. It is necessary to repeat that 7 of the 15 cases had hypogonadotrophism associated with depression in the general level of nutrition caused by intestinal parasites. Of the remaining 8 cases, 6 had only selective absence of gonadotrophins the cause of which remains undetermined. Hypo-ovarianism is reflected in the changes in the vaginal cytology which is probably the best practical method of assessing the level of circulating oestrogen (Shah, 1952). Thus 13 of the 15 cases had marked to moderate oestrogen deficiency. It is, however, important to mention that, even if all these cases had normal pituitary-ovarian function, yet, in 8 cases at least the uterus was of such a small size that most probably it would not have responded to the normal oestrogenic titre to initiate menstruation (Table III).

Table III

HYPOGONADOTROPHISM (15)

CLINICAL GROUPS	VAGINAL CYTOLOGY				UTERUS IN cms				ETIOLOGY
	N	D-1	D-2	D-3	>5·0	<5·0	<2·5	R	
S.I. (7)	–	1	1	5	–	–	3	1	NUTRITIONAL
					NOT MEASURED			3	2 Giardia Lamblia 4
									1 Ascaris Lumbricoides 1
S.H. (6)	–	–	6	–	1	1	3	1	NUTRITIONAL
									2 Ascaris Lumbricoides 2
									IDIOPATHIC 4
N.S.D.(2)	–	1	1	–	1	1	–	–	IDIOPATHIC 2

N – Good oestrogenic effect
D-1 – Minimal oestrogen deficiency
D-2 – Moderate oestrogen deficiency
D-3 – Marked oestrogen deficiency
R – Rudimentary or absence

There are only two cases of primary hypo-ovarianism among these

patients (Table II). In striking contrast to secondary hypo-ovarianism caused by hypogonadotrophism, relatively large amounts of gonadotrophins were present in the urine of both these cases. Thus the estimation of urinary gonadotrophins is the only differentiating marker between primary hypo-ovarianism caused by intrinsic structural or functional defects of the ovary and secondary hypo-ovarianism. One of them was genetically male.

The next group of 23 cases constitutes the larger single group who had some intrinsic structural or functional defect of the uterus and/or vagina. Eleven of these cases had congenital absence of uterus and/or vagina and the remaining eleven cases had acquired infection that destroyed the endometrium (Table II). The remaining one case had hardly any endometrium, in spite of the adequate pituitary-ovarian function. Large doses of oestrogen spread over a considerable period of time failed to stimulate any growth of the endometrium.

Table IV

CONGENITAL ABSENCE OF GONAD, UTERUS OR VAGINA (13)

	CLINICAL GROUPS	ANATOMICAL SEX	GENETIC SEX	ETIOLOGY
I	S.I. (4)	♀ 4	♀ 3 ♂ 1	ABSENCE OF UTERUS – 2 GONADAL DYSGENESIS – 2
II	S.H. (2)	♀ 2	♀ 1 ♂ 1	ABSENCE OF UTERUS TESTICULAR FEMINIZING SYNDROME
III	N.S.D.(4)	♀ 4	♀ 2 ♂ 2	ABSENCE OF VAGINA & UTERUS ABSENCE OF VAGINA & NORMAL UTERUS TESTICULAR FEMINIZING SYNDROME
IV	A.S.D.(3)	♀ 1 Ambiguous 2	♂ 3	TESTICULAR FEMINIZING SYNDROME INCOMPLETE T. F. SYNDROME MALE PSEUDOHERMAPHRODITISM

The etiological factors involved in the group of cases having congenital defects of the gonad, uterus and/or vagina are shown in Table IV. It is evident that such cases are more or less evenly distributed in all the four clinical groups. Eleven of these 13 cases had anatomically female external genitalia while the remaining two had ambiguous genitalia. It is interesting to mention that 5 of the 11 cases having anatomical sex of female were found to be genetically male. Unless the genetic sex is determined in all the cases of primary amenorrhoea these cases, clinically indistinguishable from genetic females having congenital absence of uterus or vagina would remain undetected (Fig. 3). Four of these 5 cases were phenotypically female having the male sex chromatin pattern. These cases therefore fall under the category of "Testicular Feminisation Syndrome" which is one of the variants of male pseudohermaphroditism. One of the four cases of "Testicular Feminisation Syndrome" deserves special mention as, unlike the cases reported so far in the literature, we failed to find testes in the abdomen (traced up to the region of kidneys), in the inguinal region or at or near external genitalia. The pelvis was completely devoid of any remnants of Wolffian or Mullerian ducts. This patient was excessively tall for her age of 17 years. The detailed case report of this patient will be published elsewhere (Shah and Shirodkar, unpublished data).

In the other six cases there was however no discrepancy between the anatomical and genetical sex. Here again there was absence of uterus in five cases. The remaining one case on the other hand, had normally functioning pituitary-ovarian-uterine axis but because of total absence of

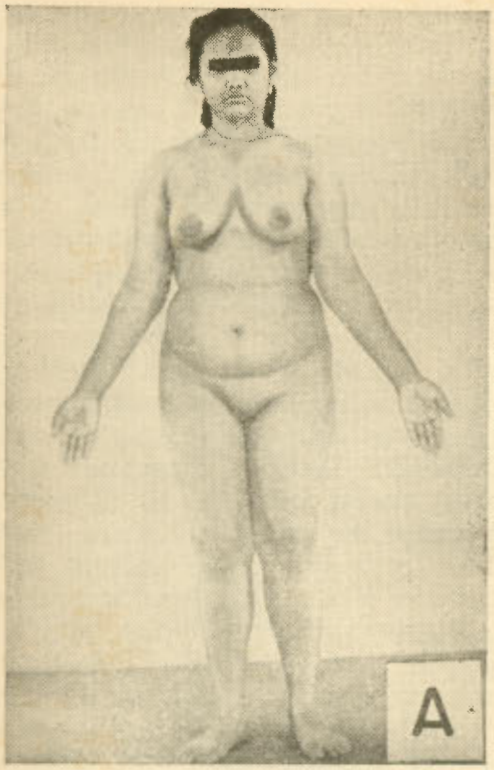

Fig. 3(A).

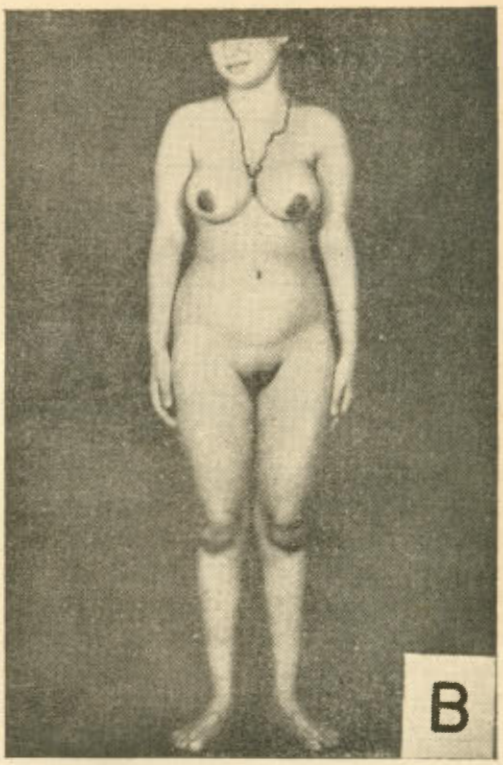

Fig. 3(B).

Fig. 3(A), 3(B)—Both these patients show normal feminine habitus and excellent breast development. The dark pigmentation of the areola in the patient (B) is due to the exogenously administered "oestroprogyn" to produce withdrawal bleeding. Both of them lacked uterus; the patient (B) has also absence of vagina. The genetic sex of the patient (A) however was male and of the patient (B) was female.

vagina she was cyclically bleeding in the peritoneal cavity. This particular case, after creation of an artificial vagina by Dr. Shirodkar, was known to menstruate through this passage for a couple of months.

It is pertinent to mention that the absence or presence of a very small uterus (less than 2.5 cm.) was seen in 22 of the 44 cases studied and the causative factors varied from genetic to acquired infection. We hardly possess, at present, any knowledge of the factors which control the development of the uterus in the embryonic life. Furthermore, the common experience that such rudimentary uteri do not respond to any amounts of adult hormones discourages many a physician to treat them with hormones.

Perhaps an equally important observation of our study is that 16 of 20 cases belonging to the Normal Sexual Development group had some defect of uterus and vagina which appeared to be responsible for the absence of menarche (Table V). Of these 16 cases, 8 had histological evidence of tuberculous endometritis and 3 had strong suspicion for the presence of this infection as definite history of

The decrease in the size of the uterus in 10 of the 11 cases appears to be a sequela of tuberculous infection and therefore whenever this finding is accompanied with nearly normal ovarian function in amenorrhoric women, primary or secondary, one should suspect this possibility unless proved otherwise (Shah, 1955).

Summary

The results of the investigations carried out on 44 patients of primary amenorrhoea reveal that

(i) Intestinal infections, especially with protozoa-like Giardia lamblia, were not infrequently seen in the "Sexual Infantilism" group. In presence of such infection it appears that optimal nutritional level for normal pituitary function is not attained.

(ii) Functional hypopituitarism was found in 8 of 9 cases of "Sexual Hypoplasia". In 5 of these 8 cases hypopituitarism was selective in gonadotrophin deficiency only.

(iii) Gross defect of uterus and/or vagina and tuberculous infection of the endometrium were responsible for absence of menstruation in 16 of 20 cases having "Normal Sexual Development". Early recognition of this infection and adequate treatment would make all the difference to such cases.

(iv) Endocrine entities and intersexual conditions, like congenital adrenal virilism (1), testicular feminisation syndrome (5), gonadal dysgenesis (2), male pseudohermaphroditism (1), were not infrequently met with.

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