

SERUM GONADOTROPHIN AND OVARIAN HISTOPATHOLOGY IN PRIMARY AMENORRHOEA

by

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Introduction

Primary amenorrhoea is not a disease but a symptom denoting derangement at any level of the hypothalamo-pituitary-ovario-uterine axis. Gonadal dysgenesis, chromosomal abnormalities and Mullerian duct defects are important aetiological factors in primary amenorrhoea. In our country, tuberculosis comes next and is probably one of the commonest causes of primary amenorrhoea where no genetic or anatomical defect can be found (Bhargava and Madan, 1969). During the year 1976, 65 patients forming 0.6% of all the patients attending the Gynaecological Out-Patient Department at All India Institute of Medical Sciences Hospital presented with primary amenorrhoea. The age for concern in primary amenorrhoea is not

unanimously agreed upon (Purandare, 1945; Israel, 1959; Deshpande *et al*, 1966; Ramaswamy and Naidu, 1966 and Singh, 1972). In our institute, the patients are investigated at any age they present, but the treatment is instituted only after the age of 18 years. Carefully planned investigations pertaining to all levels of the pituitary-ovario-uterine axis are carried out to pin-point the exact aetiological factor causing primary amenorrhoea, so that successful and effective treatment can be instituted. Hormonal studies and ovarian biopsy form an important part of the battery of investigations to reach the crux of the problem. It has been shown that radioimmunoassay of serum FSH (Follicle stimulating hormone) has a greater diagnostic accuracy than serum LH (Ryan *et al*, 1970; Robert *et al*, 1970). Sykes and Ginsberg (1972) used laparoscopy and ovarian biopsy to assess gonadal function in primary amenorrhoea and classified the gonads as active, atrophic, resting and sclerocystic depending upon their gross appearance. Goldenberg *et al* (1973) combined radioimmunoassay of gonadotrophins and laparoscopic ovarian biopsy in patients of amenorrhoea and showed that high serum FSH values reli-

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ably predicted the absence of primordial follicles. On the other hand, Jones *et al* (1969) found 3 cases of primary amenorrhoea where high serum FSH values were associated with ovaries having a number of primordial follicles but only some of them reaching upto the antrum stage. They considered these patients as depicting a separate syndrome which was either due to biologically inactive FSH or due to resistant follicular apparatus.

Material and Methods

All the patients presenting with primary amenorrhoea were referred to the Gynaecology Endocrine Clinic of the A.I.I.M.S. Hospital. These were worked up according to a protocol which included a detailed history, examination and all the investigations including serum gonadotrophin estimation and ovarian biopsy by laparoscopy or laparotomy. Two or three serum FSH estimations in every patient were done by LER 907 (Double antibody) method (Jha *et al*, 1978). Goldenberg *et al* (1973) suggest that one estimation is sufficient but to eliminate the possibility of misdiagnosis, two serum FSH estimations should be done. It is very important to have the values in the laboratory standardised because different values are obtained with different antisera (Cargille *et al*, 1968). The normal values for serum FSH in our laboratory is 150 ng/ml LER 907 (lowest in the cycle) to 400 ng/ml LER 907 (highest in the cycle). Laparoscopy and wherever necessary laparotomy was done to take ovarian biopsy. The gross appearance of ovaries was noted and the histopathological examination of the ovarian tissue was done.

In this report only 25 patients who have had estimations of serum FSH along with

the histopathological examination of ovaries, are being presented.

Results

Distribution of patients in relation to age is shown in Table I. Maximum number of patients were in the age group of 21-25 years.

TABLE I
Age Distribution

Age Group	No. of patients
15-20	5
21-25	12
26-30	6
31-35	2

Table II shows distribution of patients in relation to development of secondary

TABLE II
Secondary Sex Characters

Secondary Sex Characters	No. of patients
Well developed	3
Not developed	12
Developed due to hormones	9
Ambiguous sex characters	1

sex characters. Twelve patients had fairly well developed secondary sex characters, but 9 of them gave history that the secondary sex characters developed only after the hormonal treatment given elsewhere.

Table III shows distribution of patients in relation to development of external

TABLE III
Development of External Genitalia and Uterus

Degree of Development of Ext. Gen. & uterus	Ext. Genitalia			Uterus	
	Nor-mal	Infan-tile	Ab-sent	Small	Nor-mal size
No. of Patients	22	3	2	21	2

genitalia and size of the uterus. Most of the patients had normal external genitalia and a small uterus (on palpation).

Distribution of patients in relation to gynaecography findings is shown in Table IV. Gynaecography was an impor-

TABLE IV
Gynaecography Findings

Gynaeco- graphy findings	Ovaries			Uterus		
	Not seen	Small	Nor- mal	Not seen	Small	Nor- mal
No. of Patients	7	16	2	2	18	5

tant radiological investigation, which gave a good idea about the size of uterus and ovaries. No ovarian shadow was seen in 7 patients. Six out of these 7 had streak ovaries. In the remaining 1, the ovary was covered with dense adhesions as detected

later at laparotomy. Probably the dense adhesions had made the ovaries not detectable by gynaecography. Most of the patients on gynaecography had small uterus and small ovaries.

Table V shows that distribution of patients in relation to finding at laparoscopy/laparotomy, four patients had normal or resting ovaries, 7 had streak ovaries, 9 had small sclerocystic ovaries and 1 had testes like gonads in the groin. In the remaining 4 there were dense adhesions distorting the normal anatomy. Biopsy from these adhesions showed tuberculous granulomas on histopathology later on. None of the patients had active ovaries or atrophic ovaries as described by Sykes and Ginsberg (1972).

Table VI shows serum FSH levels in relation to ovarian histopathology.

TABLE V
Gross Appearance of Gonads on Laparoscopy/Laparotomy

Resting or Normal	Streak Ovaries	Small Sclerocystic	Dense Adhesions (Ovaries not clearly visible)	Testes like gonads (in the Groin)
4	7	9	4	1

TABLE VI
Serum FSH Levels in Relation to Ovarian Histopathology

Serum FSH ng/ml LER 907	No. of Pts.	Primordial Follicles Absent	Follicles present with no evidence of maturation	Biopsy within normal limits	Stein- Leventhal syndrome	Hypo- plastic testes
Normal (150-400)	6			5*		1
Low (less than 150)	11	1	8**	1	1	
High (400-3000)	8***	8				

* Three out of these had genital tuberculosis.

** Two cases had genital tuberculosis.

*** All patients had serum FSH levels more than 1000 ng/ml LER 907.

Discussion

Most of the patients belonged to the age group of 21-25 years (Table I). Ramaswamy and Naidu (1966) also received bulk of their patients in the same age group. It is apparent from the history and appearance of secondary sex characters following treatment elsewhere, that most of the patients kept on seeking advice and treatment elsewhere, before they reached the specialised centre for investigation (Table II). Gynaecography was an important investigation in studying the internal reproductive generative organs. Laparoscopy/laparotomy has been of great use in the diagnosis of tuberculosis of the genital tract. All the 5 patients of genital tuberculosis in the series had negative endometrial biopsy. If laparoscopy/laparotomy had not been done, definitive diagnosis could have been missed.

Correlation of Serum FSH and Ovarian Histopathology Normal Serum FSH: There were 6 cases with normal FSH. One of them had testicular feminization. The remaining 5 had normal ovarian histology with evidence of ovulation in 3 cases. The reason for amenorrhoea was genital tuberculosis in 3 patients; Mullerian duct failure in 1 patient and probably delayed menarche in the fifth patient because all her parameters were normal.

Low Serum FSH: There were 11 patients with low Serum FSH. Eight of them showed presence of follicles with no evidence of maturation. Thus these patients probably had pituitary gonadotrophic insufficiency. One patient had a chromophobe adenoma of the pituitary which was operated, following which she had pituitary insufficiency.

In 1 patient there was evidence of follicular maturation even though the FSH levels were below normal limits.

One patient with low FSH values had ovarian histopathology consistent with Stein-Leventhal Syndrome. She showed a rise in the serum oestradiol values after biopsy while the FSH values remained the same.

The remaining patient deserves special mention. She had no follicles in the ovary and the FSH levels were low despite the absence of a negative feed back mechanism.

High Serum FSH: There were 8 patients with high FSH levels. All these patients had primordial follicles conspicuously absent on histopathological examination of the ovarian tissue. This hundred per cent correlation between high serum FSH values and the absence of primordial follicles on ovarian histopathology is a very significant finding. High values of serum FSH were indicative of the absence of follicles as also suggested by Goldenberg *et al* (1973). A number of workers have shown that serum FSH radioimmunoassay has a greater diagnostic accuracy in gonadal dysgenesis and it rises more convincingly than LH. Two serum FSH estimations are preferable to reduce the possibility of misdiagnosis. We have not come across any case similar to those described by Jones *et al* (1969) and Starup *et al* (1971) where high serum FSH was associated with follicles in the ovary.

The study is of importance in identifying patients with or without primordial follicles in the ovary before attempting any surgery or induction of ovulation. Ovarian biopsy in patients without follicles (as indicated by high values of serum FSH radioimmunoassay) can be obviated. If the norms and standards of the laboratory are well established, high values of serum FSH along with low values of serum oestradiol, with well supporting

clinical evidence and cytological findings of oestrogen deficiency predict the absence of follicles in the ovary. Such patients can be spared the anaesthetic, operative and post-operative risks and complications of laparotomy or laparoscopy. In addition an abdominal scar, however small, can be avoided. The significance of avoiding surgery increases several fold as it has no therapeutic advantage, as nothing much can be done for these patients from the treatment point of view.

Low and normal values of serum FSH, however, justify diagnostic laparotomy and laparoscopy not only to decide the definite line of treatment but also to diagnose cases of tuberculosis not detected by endometrial biopsy.

Summary

Serum FSH radioimmunoassay and ovarian biopsy were done in 25 patients of primary amenorrhoea. Patients with low serum FSH values showed lack of maturity of follicles in ovarian histopathology whereas patients with high serum FSH values had no primordial follicles in the ovary. It is suggested that patients with high serum FSH values particularly with ovaries not visualized on gynaecography or with low oestradiol level and no oestrogen activity, may not be submitted to ovarian biopsy. On the other hand 3 patients out of four with normally developed genital organs and normal FSH had tuberculosis which was detected only by ovarian biopsy.

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