PREMATURE OVARIAN FAILURE

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Introduction

Whenever the ovaries are exhausted of all their endowed ova, the woman passes into a phase of menopause. This is physiological at the age of about 45 years. When it occurs before the age of 40 years, the condition is premature menopause. Though the incidence of this syndrome is not very rare, comparatively few cases are reported in world literature. This may be because of difficulties in diagnosis and women who have completed their child bearing may not report about early cessation of menstruation.

Three typical cases of premature menopause proved by ovarian histopathology and two cases proved by urinary gonadotrophins estimation are reported here (Table I).

These cases were collected over a period of 4 years. Bjoro (1962) diagnosed 7 cases of premature menopause by persistently raised urinary gonadotrophin levels among 125 cases of oligomenorrhoea. Keettle and Bradbury (1964) reported 25 cases of premature menopause among 425 cases of primary and secondary amenorrhoea. Recently, Moraes-Ruehsen and Jones (1967) reported 21 cases of premature ovarian failure in 300 cases of secondary amenorrhoea. Troll *et al.* (1961) report the incidence as 11% in 76 cases of secondary amenorrhoea. Jones and Nalley (1959) gave the incidence as 6%. Age of these patients varied from 21 to 36 years. We cannot give the exact incidence of this entity because the gonadotrophin estimations were available in very few selected cases. Keettel and Bradbury (1964) have reported 16 years as the earliest age of onset of this condition. Bjoro's patients were between 23 and 32 years of age. Age of menarche in our patients varied from 13-15 years. One patient did not remember exactly the age of menarche.

Duration of secondary amenorrhoea in the patients varied from 6 months to 7 years. Menstruation continued for some years regularly or irregularly before they passed into a phase of amenorrhoea. Sudden cessation of menstruation occurred in only one of our patients. Menstruation was grossly abnormal from menarche onwards in two of our patients. One of these had only three menstrual periods from menarche onwards. In the other two patients normal menstruation was replaced by a phase of oligomenorrhoea, menstruation coming at the interval of 3 to 4 months for 2-3 years before the present onset of amenorrhoea.

All our patients had primary sterility. This may be because patients with pri-

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TABLE I

Premature Menopause—Important Points of History and Investigations

Case No.	Age in years	Secondary amenorrhoea Duration	Sterility	F.M.P.	Pa. M. C.	V. Smear	Endometrial biopsy	Culdoscopy	Urinary gonado-trophins	Ovarian biopsy
1.	21	1/2 year	Primary	13	1–3 / 3–6 m.	Moderate hypotrophy	V. scanty	Streak ovaries	—	No primordial follicles
2.	22	7 years	Primary	14	3 / 2 m.	Mild atrophy	Proliferative	Streak ovaries	—	No primordial follicles
3.	27	4 years	Primary	14	3 , 3 / 22 3 m.	Moderate hypotrophy	Proliferative	Atrophic	—	No primordial follicles
4.	36	4 years	Primary	15	7–8 / 22–25 2–4 / 3–4 m.	Moderate atrophy	Proliferative	—	AB High	—
5.	35	2 years	Primary	?	3 / 30	Moderate hypotrophy with few parabasal cells.	Proliferative	Right atrophic left smaller than normal	AB High	—

(Abnormally high titre, definitely indicating menopause).

mary sterility and amenorrhoea attended the clinic regularly and were also investigated more thoroughly, a point very essential for the diagnosis of this condition.

Some of the Keetle and Bradbury's patients with premature menopause had conceived, but none of the Klinch *et al's* (1965) patients ever conceived.

Eighty five per cent of Moraes-Ruehsent's (1967) patients complained of hot flushes. Perloff and Schneberry (1957) also consider hot flushes as the beginning of the syndrome. However, even after direct questioning this important history was given by only one of our patients. Patients of Klinch *et al.* also did not complain of hot flushes. Dyspareunia was complained of by only one patient. None of these patients had a positive family history of premature menopause.

No abnormality was detected on general or systemic examination. There was no evidence of any other endocrinopathy. They all had normal blood pressure. The vagina and uterus usually show the first sign of oestrogen deprivation. The vagina showed atrophic changes in only two of our patients. Uteri were smaller than normal size in all our patients. There was evidence of loss of secondary sex characters in one patient. The other 2 cases had hypoplastic breasts. Vaginal smears in our patients varied from mild and moderate atrophy to moderate hypotrophy without any cyclic variation. Since vaginal smears were used for hormonal evaluation, oestrogen estimations were not done. Progestorone test was negative in all our patients. Proliferative phase of the endometrium was obtained in 4 patients after hormonal priming and 1 patient had scanty endometrium. All these patients had withdrawal bleeding after oestrogen therapy.

Culdoscopic examination was done in 4 of our patients. Both the ovaries were streak-like in two patients. One patient had both ovaries atrophic and the other one had one ovary atrophic and the other smaller than normal.

Urinary gonadotrophin estimations were done in two patients as a single estimation. The levels were abonrmally high.

Exploratory laparotomy and ovarian biopsy from both the ovaries was done in 3 patients. Ovaries were small, streak-like, wrinkled. No primordial or cystic follicles were seen. There was only ovarian stromal tissue (Fig. 1).

Clomiphene citrate or pituitary gonadotrophins are not useful in patients with premature menopause (Kistner, 1965). As the diagnosis of this condition is very useful in patients with amenorrhoea and sterility, a few points about the method of diagnosis should not be out of place. According to Israel (1967) diagnosis of premature menopause is often impossible with the aid of best of the laboratory procedures. High urinary gonadotrophins is considered as the key to the diagnosis by many authors.

The second way to diagnose the condition is by the ovarian stimulation test. Kupperman (1963) gives 500 I. U. pregnant mare's serum intramuscularly thrice a week for 3 weeks. Increased vaginal cornification, increase in size and tenderness of breasts and calamenia or increased sanguineous vaginal discharge taking place following 100 mgm. of proluton depot given five days after the last pregnant mare's serum injection, indicate a positive ovarian response. Cox *et. al.* (1967) prefer human gonadotrophins to pregnant mare's serum. He gives three ampoules of pergonal each day for 3 days. 15-40 ug. of urinary oes-

trogen level is an indication of satisfactory response.

The third method is by ovarian biopsy. This is not practical in all cases, yet with this it is possible to diagnose the condition in those centres where gonadotrophin estimations are not available.

Aetiology

Aetiology of this condition is obscure. Beclare and Simmonet (1963) attribute it to hypergonadotrophic state of hypothalamo-pituitary axis. This imparted a faster pace to the process of follicular growth and atresia of the ova. It may also be due to deficient number of ova in the ovaries (Johnston *et al.*, 1961).

Recently it is shown that the condition is often associated with chromosomal abnormality. This is shown by various authors. Gordon (1967) reported xo/xx/xxx/xxxxx mosaicism. Jacob *et al.* (1959) reported triple X syndrome leading to premature menopause. Moraes-Ruchsen (1967) found one patient with xo/xx Karyotype among 16 patients of premature menopause in whom the buccal smear was examined. The case was selected for chromosomal study because of low percentage of Barr bodies.

Treatment

Cyclic hormone therapy was advised for all the patients to prevent defeminisation, dyspareunia, cardiovascular diseases and hypertension. Our patients were not followed up for a long time to evaluate the presence or absence of these complications. Sznasderman and Oliver (1963) noticed that cardiovascular diseases were 7 times more common in patients with this type of amenorrhoea. Klinch *et. al.* (1965) also recommend oestrogen or progestational compounds for these patients.

Summary

Five patients with premature menopause are described in detail along with review of literature.

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References

1. Beclare, C. and Simmonet, H.: Presse Med., **71**: 3, 1963.
2. Bjoro, K.: Acta Obst. & Gynec. Scandinav., 5 (**Supp. 6**): 41, 1962.
3. Cox, R. I., Cox, L. W., Black, T. L.: (Ovarian function Tests) Proceedings of the Third Asia and Oceania Congress of Endocrinology, Manila, January 1967. Part II, Ed. by Litonjua, A. D., p. 763.
4. Gordon, D. L. and Paulsen, A.: Am. J. Obst. & Gynec. **97**: 85, 1967.
5. Israel, S. L.: Menstrual disorders and Sterility, Ed. by Israel, S. L., Hoeber Medical Division, New York, 1967, p. 252.
6. Jacob, P. A., Baik, A. G., Corte Brown, W. H. and Strong, J. A.: Lancet, **1**: 710, 1959.
7. Jhonston, A. W., Ferguson, Smith, M. A., Handmaker, S. D., Jones, H. W. and Jones, G. S.: Brit. Med. J. **2**: 1046, 1961.
8. Jones, G. E. S. and Nally, B. W.: Fertil and Steril. **10**: 461, 1959.
9. Keettel, W. C. and Bradbury, J. T.: Am. J. Obst. & Gynec. **83**: 89, 1964.
10. Kisthner, R. W.: Am. J. Obst. & Gynec. **92**: 380, 1965.
11. Klinch, R. A. H., Plunkett, E. R. S., Mout, M. S. and Carr, D. H.: Am. J. Obst. & Gynec. **91**: 630, 1965.
12. Kupperman, H. S.: Human Endocrinology, Part I, Hexton, Blackwell

Scientific Publications, Oxford, 1963, p. 244.

13. Moraes Ruehsent, M. and Jones, G. S.: Fertil. & Steril. 18: 440, 1967.

14. Perloff, W. H. and Schneberry, N. G.: Am. Practit. 8: 1955, 1957.

15. Sznasderman, M. and Oliver, M. F.: Lancet. 1: 962, 1963.

16. Troll, D., Sele, V. and Johnson, S. G.: Human Pit. Gohadotropins, Albert, A., Springfield (III), Charles C. Thomas, 1961.

See Fig. on Art Paper IV