BIOPATHOLOGICAL IMPACT OF NORMAL MENSTRUATION FOR MANY YEARS ON OVARIAN AND TUBAL FACTORS OF INFERTILITY

by

B. N. CHAKRAVARTY,* M.O. (Cal.), F.R.C.O.G. (Lond.)

and

Late SUBHAS MUKHERJEE,** M.B.,B.S., Ph.D. (Edin.), Ph.D. (Cal.)

Introduction

While investigating a series of infertile women it was observed that the incidence of premature ovarian senility and apparently unexplained tubal defect increased significantly with advancing age in women who were primarily infertile. From this observation it appeared that prolonged cyclic activity of the hypothalamic gonadal axis resulting in uninterrupted normal and regular menstruation for many years could perhaps be related etiologically to ovarian and tubal factors of infertility. It is possible that such prolonged and cyclic activity of the hormonal axis on one hand and the target organs on the other, may bring about premature senility of the ovarian function and in addition, can cause tubal dysfunction by inevitable retrograde reflux of blood during each menstrual cycle.

Objective

The objective of the present communication is to evaluate the validity of this concept based on experimental study of ovarian activity following interrupted and uninterrupted menstruation for several years supplemented by relevant clinical data of infertile women of two age groups: one group relatively young experiencing less number of menstrual cycles and the other, comparatively older, who had numerous menstrual episodes during their barren reproductive life.

Experimental Observation

A pilot study was conducted on two groups of women with a view to ascertain the impact of recurrent menstrual cycles for prolonged period of time on ovarian activity.

(a) Twenty-two grande multiparous women in the age group 41-43 years; that is so called in "women approaching menopause". Each of them experienced on an average approximately 19-20 menstrual episodes during their 41-43 years of life. The results were compared with:

(b) Eighteen nulliparous women aged between 41-43 years experiencing regular recurrent menstrual cycles for about 30 years (approximately 350 menstrual episodes during their 41-43 years of life). All these women happened to be the wives of azoospermic husbands seeking consultations for infertility of more than 10 years duration. Primarily, these women had apparently normal reproduc-

*Professor, Obstetrics and Gynaecology, N.R.S. Medical College, Calcutta.

**Ex-Professor, Deptt. of Physiology, R. G. Kar Medical College, Calcutta.

Accepted for publication on 16-10-81.

tive function (reports collected from records).

The status of ovarian activity was evaluated by two methods:

(i) Serial estimation of urinary oestrogen and urinary luteinising hormones (LH) in fraction—pooled 7 days samples performed through one complete cycle.

(ii) Ovarian response (by steroid output) to fixed dosage of human menopausal gonadotrophins. The results are given in Table I & II.

TABLE I

Mean Urinary Excretion of Gonadal and Gonadotrophin Hormone in Grande-multiparous and Nulliparous Women

	Grande Multipara	Nullipara
LH (1.U. 2nd IRP per 24 hours)	2.8 ± 1.1	11.7 ± 4.9
Oestrone (mcg/24 hours)	7.8 ± 2.7	7.3 ± 3.6

TABLE II

Mean Urinary Excretion of Oestrone Following Standard Test Dose of Exogenous Gonadotrophins

	Grande multipara	Infertile Nullipara
Oestrone	18.7 ± 4.8	10.3 ± 3.5

Clinical Observation

Two thousand three hundred and forty-eight women with primary infertility were investigated during the period from January, 1974 to December, 1980. Tubal factor was involved in 608 and ovarian in 323. Those with secondary infertility were not included in the present study.

In order to assess exclusively the possible adverse effects of menstruation for prolonged period of time on ovarian and tubal factors other detectable and possible causes of ovarian and tubal infertility were carefully sorted out and excluded. With the same object, the relative incidence of ovarian and tubal infertility were compared in women of two age groups;—women below 25 and those above 25 years. Twenty-five years has been considered as the ideal dividing line because fertility status of women is maximum between 15 to 35 years. Therefore, women of comparable fertility potential in the two age groups having variable degree of biopathological impact of normal menstruation for shorter and longer periods of time can be conveniently compared and evaluated. Table III shows the number of women with ovarian and tubal defect in these two age groups.

TABLE III

Tubal and Ovarian Defect in Two Age Groups

Age in years	Number	Ovarian factor	Tubal factor
Age less than 25	942	82 (8.7%)	97 (10.4%)
Age more than 25	1406	241 (17.1%)	511 (36.3%)
Total:	2348	323 (13.8%)	608 (25.8%)

Ovarian Factor

Ovarian factors involved with infertility in the present series were detected in 323 women. Excluding non-ovulation due to endocrinal dysfunction of the potentially functioning ovaries, ovarian endometriosis, corpus luteum inadequacy and surgical resection of ovaries for neoplastic and non-neoplastic conditions, the incidence of non-ovulation due to apparently unexplained premature ovarian failure in the two age groups is shown in Table IV.

The diagnosis of premature ovarian failure was based on (a) Clinical history, (b) abnormally high level of serum

TABLE IV

Age group in years	Ovarian factors involved	Premature ovarian failure
Less than 25	82	1
More than 25	241	14

gonadotrophins determined by Radioimmunoassay, (c) laparoscopic examination, and in few cases by (d) examination of serial vaginal cytohormonal pattern (CHP) and cervical mucus unit (CMU) following induction with standard fixed dosage of gonadotrophins and (e) ovarian biopsy. Details are given in Table V.

Tubal Factor

Six hundred and eight women had tubal defect. The methods of diagnosis of tubal defect are given in Table VI.

TABLE VI

Methods of diagnosis	No. of cases
Clinically adnexal or uterine lump palpable	62
Hysterosalpingogram	546
Laparoscope	136

Hysterosalpingogram was not performed in cases where uterine or adnexal lump was palpable. In these and in women where hysterosalpingogram demonstrated controversial report, tubal

TABLE V
Diagnosis of Premature Ovarian Failure

Methods of diagnosis	No. of cases	
	Less han 25 years	More than 25 years
Clinical:		
Secondary amenorrhoea	1	14
Hot flushes	Nil	10
RIA:		
Estimation of gonadotrophins FSH	1	14
(Normal 5-20 mIU/ml.)	60 mIU/ml.	Range 70-108 mIU/ml.
LH		
(Normal 5-30 mIU/ml.)	55 mIU/ml.	Range 60-110 mIU/ml.
Cytohormonal:		
No change in serial vaginal CHP and CMU after induction with gonadotrophins (Pergonal—Serono, FSH-75 IU) LH-75 IU)	1	5
Laparoscopic Examination:		
Wrinkled streak-like gonads	1	10
Ovarian biopsy:		
No primordial or cystic follicles; only ovarian stroma.	—	5

competence was tested by laparoscopic examination with or without chromopertubation. Diagnosis of tubercular involvement was based on hysterosalpingographic observation of intrauterine adhesion in the absence of history of previous abortion or curettage, narrowing and 'beaded' appearance of the tube, laparoscopic finding of tubercules and histological evidence of tubercular endometritis with or without a palpable adnexal lump.

Detectable Factors of Tubal Pathology

These customary parameters for detecting tubal defect could identify the possible etiological factors in approximately 33 per cent of women investigated (205 out of 608 cases—Table VII). The etiology of

TABLE VII
Detectable Factors for Tubal Pathology
(20 *Cases*)

	Below 25 years	Above 25 years
Endometriosis	12	41
Tuberculosis	18	5
Tubo-ovarian mass and pelvic adhesion	20	43
Fibroid	5	14
Previous laparotomy resulting in tubal adhesion/occlusion	15	32
Total:	70	135

tubal dysfunction in the rest, remained apparently unexplained.

Apparently Unexplained Tubal Defect

The exact etiology of tubal defect in 403 women with primary infertility could not be detected. Table VIII further demonstrates that the incidence of apparently unexplained tubal dysfunction was higher in women above the age of 25

TABLE VIII

Age in years	Total No. of cases	No. of cases with apparently unexplained tubal defect
Less than 25	942	27 (2.8%)
More than 25	1406	376 (26.7%)

compared to those who were less than 25 years old.

Discussion

In our experimental study, marked differences with regard to the status of ovarian function was observed when grand multiparous women passing through long periods of amenorrhoea due to repeated pregnancy and lactation were compared with comparable group of nulliparous women experiencing regular cyclic menstruation throughout the major period of their reproductive life. Significantly higher proportion of such nulliparous women showed distinct evidence of earlier ovarian senility, as judged by the levels of urinary LH and urinary steroid evaluation.

In the clinical evaluation of infertility work up, 14 women above the age of 25 years had premature ovarian failure and only 1 below the age of 25 had similar problem. According to Israel (1967) diagnosis of premature menopause is often difficult even with the aid of best of the laboratory procedures. Speroff *et al* (1979) believe that serum FSH levels in the post menopausal or cast rate range is the most reliable evidence of ovarian failure. Vaidya and Purandare (1972) however have stressed on 3 parameters for the diagnosis of premature ovarian failure. Persistently high level of urinary or plasma gonadotrophins, ovarian stimu-

lation test using ovulation inducing drugs and ovarian biopsy are reasonable reliable evidences of premature ovarian senescence. In the present study all these parameters were considered.

Various theories have been put forward to explain premature menopause. Beclare and Simmonet (1963) believe it to be due to hypergonadotropic state of hypothalamic pituitary axis—leading to faster pace to the process of follicular growth and atresia of the ova. Johnson *et al* (1961) believe this syndrome to be due to deficient number of ova in the ovaries. Gordon and Paulson (1967); Jacob *et al* (1959) and Moraes Ruchsen and Jones (1967) found chromosomal anomaly associated with premature menopause.

Leaving aside chromosomal anomalies, it appears from our observations that abstinance from conception either by choice or by circumstances is perhaps one of the major contributory factors for premature ovarian failure. The regular recurrence of ovulatory menstrual cycles for many years in nulliparous women, each cycle resulting in the atresia of a large number of follicles bring about early senility of ovarian function. In the grand multiparous women on the other hand, it is possible that during successive pregnancy and lactation, the relatively nonfluctuating steady state of ovarian activity associated with steady and tonic functioning of the hypothalamic-pituitary gonadal axis might be instrumental in preserving the otherwise inevitable atresia of large number of ovarian follicles. In other words, the whole process of follicular activity is temporarily kept in abeyance or retarded during pregnancy and lactation, as if this was temporarily sent to 'cold storage'.

As women are born with fixed number of follicles, eventual atresia of all the available follicles would result in irreversible cessation of all the ovarian function—the whole process ushering in premature menopause. Therefore, leaving aside other causes of infertility, it seems very likely that cyclic recurrence of regular menstruation for many years is inherently associated with the problem of relatively premature ovarian senility.

With regard to the tubal factor in primary infertility it has been observed in the present study that in women above the age of 25, tubal factor was involved in 26.7 per cent against 2.8 per cent in women below the age of 25 years. These figures exclude those with apparently detectable causes of tubal infertility like tuberculosis, specific and non-specific tubal infection, mechanical block by cornual fibroid or endometriosis and tubal distortion by previous pelvic surgical procedures.

It is possible that such tubal block in nulliparous women in the absence of a palpable or concievable pathology could be the effect of retrograde flow of menstrual blood resulting from reccurrent cyclic menstruation for many years. Sampson's (1922) original view of retrograde menstruation in the histogenesis of pelvic endometriosis is still popularly accepted. The experimental work of Geist (1933) demonstrated without question that clumps of endometrial cells with menstrual blood flow in a retrograde manner from the uterine cavity through the minute lumen of the intestitial portion of the oviduct.

There are many reports of conception in infertile women immediately following the investigative procedures of tubal insufflation or hysterosalpingogram (tubal washing). Success achieved in these cases could possibly be due to removal of the

mechanical block in the tube presumably caused by temporary plug formed by organised menstrual blood.

These reports support our clinical observation and it seems very likely that retrograde menstrual flow for prolonged period of time could lead to salpingopathic infertility due to either mechanical block, endosalpingitis or endosalpingiosis. Repeated reflux of menstrual blood may gradually damage the mucous membrane and muscular layer of the tube—not primarily causing tubal block but leading to a state of non-occlusive tubal dysfunction—ultimately resulting in tubal infertility.

It appears that even at present many cases of female infertility associated with apparently patent but physiologically incompetent oviducts are being misdiagnosed and misinterpreted.

Summary and Conclusion

1. Biopathological impact of normal cyclic menstruation for many years on tubal and ovarian factors of infertility has been evaluated.

2. Prolonged cyclic and therefore fluctuating activity of the pituitary gonadal axis concurrently functioning with recurrent menstrual episodes may lead to atresia of large number of ovarian follicles during each menstrual cycle—ultimately leading to premature failure of ovarian function.

3. Moreover, in these women, it is also possible for the tubes to be gradually blocked or damaged by repeated reflux of blood and endometrial debris inside the tubal lumen during each menstrual cycle.

4. Therefore, it seems likely that cyclical menstruation for many years resulting from late marriage followed by use of contraceptive measures for few years and then failure to identify and correct a reversible defect in the initial years of infertility investigation may eventually have an adverse effect on ovarian activity and tubal function ultimately leading to a state of irreversible infertility.

References

1. Beclare, C. and Simmonet, H.: Presse. Med. 71: 3, 1963.
2. Geist, S. H.: Am. J. Obstet. Gynec. 25: 751, 1933.
3. Gordon, D. L. and Paulson, A.: Am. J. Obstet. Gynec. 97: 85, 1967.
4. Israel, S. L.: Menstrual disorders and Sterility, 3rd ed. Hoeber Medical Division, New York, P. 252, 1967.
5. Jacob, P. A., Balk, A. G., Corte Brown, W. H. and Strong, J. A.: Lancet. 1: 710, 1959.
6. Johnson, A. W., Ferguson, Smith, M. A., Handmaker, S. D., Jones, H. W. and Jones, G. S.: Brit. Med. J. 2: 1046, 1961.
7. Moraes Ruchsen, M. and Jones, G. S.: Fertil. and Steril. 18: 440, 1967.
8. Sampson, J. A.: Arch. Surg. 5: 217, 1922.
9. Speroff, L., Robert, H. G. and Nathan, G. K.: Clinical Gynaec. Endocrinology and Infertility, 2nd Ed. Williams and Wilkins, Baltimore, Maryland 21202 U.S.A. P. 379, 1979.
10. Vaidya, R. P. and Purandare, V. N.: J. Obstet. Gynaec. India. 22: 41, 1972.