PAPERS AND ORIGINALS

The significance of FSH elevation in young women with disorders of ovulation

C O'HERLIHY, R J PEPPERELL, J H EVANS

Summary and conclusions

High serum follicle stimulating hormone (FSH) values are consistent with ovarian failure. We studied the progress of 67 women aged under 35 years with oligomenorrhoea or secondary amenorrhoea in whom the serum FSH value was greater than 20 U/l. Twenty-four patients remained amenorrhoeic, but 17 ovulated and six conceived, two on two occasions. Coincident mean serum luteinising hormone (LH) concentrations were significantly lower and mean total urinary oestrogen concentrations were significantly higher in patients who subsequently ovulated, but the degree of increase in FSH did not correlate well with later ovarian function. Treatment with oestrogens, clomiphene citrate, human pituitary gonadotrophin, and bromocriptine was of no benefit in inducing an ovarian response while FSH concentrations remained raised.

Our results suggest that a considerable proportion of younger women with ovulatory disorders associated with FSH values in the menopausal range will spontaneously resume ovulation and some will conceive.

Introduction

During the normal menstrual cycle follicle stimulating hormone (FSH) and luteinising hormone (LH) concentrations follow a definite pattern with an early follicular phase peak of FSH and mid-cycle peaks of both FSH and LH.^{1,2} Single estimations of FSH provide an accurate assessment of the production of this hormone,³ and disorders of ovarian function can be characterised from the measurable serum FSH and LH values.⁴ During the follicular phase FSH concentrations rarely exceed 10 U/l and

during the mid-cycle peaks of FSH and LH, FSH values do not exceed 20 U/l and do not overlap with values seen in postmenopausal women.

The average age of menopause in women of European origin is about 50 years.^{5,6} For several years preceding the menopause FSH concentrations early in the cycle gradually rise⁷ and after the complete cessation of menses the FSH and LH concentrations remain raised. Episodic hypergonadotrophism before cessation of the menses may be followed by ovulation when FSH and LH values return to normal.⁸

About 10% of all patients presenting with secondary amenorrhoea have FSH concentrations consistent with ovarian failure.^{9,10} Some of these women are still at an age when further child-bearing is desired—for example, under 35—but, since no effective fertility treatment is available in the presence of raised FSH concentrations, a prognosis of permanent sterility is usually given. During the past decade, however, several isolated reports of pregnancies following a diagnosis of premature ovarian failure have appeared and a syndrome of "gonadotrophin resistance" has been proposed to explain these cases.¹¹⁻¹⁷

We decided to study a group of younger women with raised serum FSH values associated with menstrual disturbance to determine what proportion would resume ovarian activity and what factors might differentiate those with transient ovarian failure or resistance from those with permanent failure.

Patients and methods

Using the criterion of a plasma FSH value above 20 U/l (not mid-cycle), we retrospectively collected data on 67 consecutive patients with menstrual disturbances over the four years 1975-9. Details obtained on each patient included age, parity, age at menarche, antecedent menstrual pattern, symptoms of oestrogen deficiency (coital dryness, hot flushes), associated illness, and subsequent spontaneous resolution or response to treatment. Patients over 35 years of age were excluded, as were those with primary amenorrhoea and those who had undergone surgical castration or pelvic irradiation.

All gonadotrophin estimations were performed in the professorial unit of the Royal Women's Hospital. Serum FSH and LH concentrations were measured by standard radioimmunoassay using the reference standard preparations MRC 69/104 (FSH) and MRC 68/40 (LH). Serum prolactin values were also measured in every patient. In most patients estimates of urinary total oestrogens¹⁸ and pregnanediol¹⁹ were performed within four days of gonadotrophin measurement.

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Patients were divided into four groups according to their clinical progress in the one to five years after the discovery of the raised FSH value: those with persistent amenorrhoea; those with subsequent spontaneous menstrual-like vaginal bleeding without proved ovulation (bleeding during oestrogen-progestogen therapy excluded); those who subsequently ovulated but did not conceive; and those who subsequently conceived. Ovulation was diagnosed in the absence of conception only when a urinary pregnanediol estimation exceeded 6.24 $\mu\text{mol}/24\text{ h}$ (2 mg/24 h) in the mid-luteal phase,²⁰ or when a recent corpus luteum was identified at laparoscopy or laparotomy.

Results were analysed using the Kruskal-Wallis one-way analysis of variance combined with the Wilcoxon two-sample test to compare individual groups.

Results

Of the 67 hypergonadotrophic patients, 50 presented with secondary amenorrhoea (greater than six months' duration) and 17 with oligomenorrhoea (menstrual intervals from six weeks to six months). Twenty-four patients remained amenorrhoeic, but surprisingly 26 had further menstrual bleeding and at least four of these had endocrinological evidence of ovarian follicular development. Seventeen women subsequently ovulated and six of these conceived (two patients on two occasions).

Table I summarises the patients' details and shows that there were no significant differences between the patients with persistent amenorrhoea and those in whom ovarian function returned with regard to age at menarche, previous parity, age at time of diagnosis of raised FSH concentration, or the incidence of symptoms of oestrogen deprivation. All patients had normal serum prolactin concentrations.

TABLE I—Characteristics of 67 patients with raised FSH concentrations in relation to subsequent progress

	Persistent amenorrhoea	Vaginal bleeding	Ovulation without conception	Pregnancy
Total No of patients (%)	24 (36)	26 (39)	11 (16)	6 (9)
Mean ($\pm$ SD) age at menarche (years)	13.31 $\pm$ 1.64	13.13 $\pm$ 1.60	13.70 $\pm$ 1.63	
No previously pregnant	10	9	9	
Menstrual pattern:				
No with secondary amenorrhoea (n=50)	23	15	12	
No with oligomenorrhoea (n=17)	1	11	5	
Mean ($\pm$ SD) age at diagnosis of raised FSH (years)	28.8 $\pm$ 4.7	28.7 $\pm$ 4.3	28.2 $\pm$ 4.1	
No with symptoms (%) (flushes, coital dryness) (n=34)	14 (58)	12 (46)	8 (47)	

Oligomenorrhoeic women were more likely to have further menstrual episodes than those presenting with amenorrhoea. Patients who bled during oestrogen or progestogen treatment were not included among those who had subsequent vaginal bleeding without proved ovulation.

Most of the patients studied were free of associated illness or disease and were asymptomatic apart from their menstrual disturbance, hot flushes, or coital dryness. Two patients with blood dyscrasias (chronic myelogenous leukaemia and Hodgkin's disease, respectively) had had regular cycles before amenorrhoea, which started during cytotoxic chemotherapy and persisted after the treatment stopped. One patient with Addison's disease also suffered from hypothyroidism and oophoritis and did not ovulate during the follow-up period. Chromosome analysis was performed in only eight subjects, and one who developed persistent amenorrhoea was found to be a 44 XX/XO mosaic. Other incidental illnesses included epilepsy, diabetes, optic nerve atrophy, congenital hyperbilirubinaemia, and hyperthyroidism.

Gynaecological symptoms other than those due to oestrogen deficiency were few. Two patients were hirsute, but the problem antedated the presenting menstrual disturbance in both and neither was severely affected. Ovarian biopsy was performed in 17 cases, 10 at laparotomy and 7 laparoscopically. Six of these 17 patients had streak gonads (three unilateral). Table II shows that the presence of primordial follicles at biopsy was a relatively reliable index of subsequent ovarian function, though the numbers were too small to reach statistical significance. One patient, however, had no primordial follicles in the biopsy taken at laparoscopy but subsequently ovulated and conceived.

TABLE II—Details of serum FSH, LH, and urinary oestrogen values at time of presentation together with ovarian biopsy results. Presence of adequate primordial follicles constituted a positive biopsy

	Persistent amenorrhoea	Vaginal bleeding	Ovulation without conception	Pregnancy
Total No of patients	24	26	11	6
FSH:				
21-30 U/l (n=15)	4	6	5	
31-40 U/l (n=17)	6	6	5	
>40 U/l (n=35)	14	14	7	
FSH:LH ratio >1 (%)	16 (66.7) [†]	14 (53.8) [†]	12 (70.5) ^{††}	
*Mean ($\pm$ SD) LH (U/l)	44.2 $\pm$ 23.3 [§]	43.4 $\pm$ 20.6 [§]	29.1 $\pm$ 18.2 [§]	
**Mean ($\pm$ SD) total urinary oestrogens (nmol/24 h)	13.2 $\pm$ 15.8	28.1 $\pm$ 32.8	54.4 $\pm$ 43.56	
Positive ovarian biopsy	1/7	2/6	3/4	

* Kruskal-Wallis analysis of variance $H = 7.06$; $p < 0.05$.

** Kruskal-Wallis analysis of variance $H = 11.8$; $p < 0.005$.

[†] $p < 0.03$

^{††} $p < 0.02$

[§] $p < 0.001$

^{||} $p < 0.05$

^{|||} $p = 0.05$

[§] Conversion: SI to traditional units—Oestrogens (as oestradiol): 1 nmol/24 h $\approx$ 0.272 $\mu\text{g}/24\text{ h}$.

Total urinary oestrogen excretion was measured in 55 of the 67 patients within four days of the blood sample that showed raised gonadotrophin values. Analyses of variance showed significant differences between patients who remained amenorrhoeic, those who later menstruated, and those who subsequently ovulated in respect of both total urinary oestrogens ($p < 0.005$) and serum LH ($p < 0.05$). Although absolute FSH concentrations were of little prognostic value, fewer women with values over 40 U/l ovulated or conceived, compared with those whose FSH concentrations were below this value. Nevertheless, five of the six women who conceived were in the former group. On the other hand, the mean LH concentration in the group of 17 who ovulated or conceived was significantly lower ($p < 0.03$) than in those who did not (table II).

The incidence of ovulation or conception was no different in treated or untreated patients (table III). Of 40 treated patients, 14 received two forms of treatment, the second usually oestrogen replacement after failed ovulation induction. No patient responded to any form of treatment while FSH concentrations remained raised, but

TABLE III—Response to treatment and subsequent progress of treated and untreated patients

	Persistent amenorrhoea	Vaginal bleeding*	Ovulation without conception	Pregnancy
Total No of patients	24	26	11	6
No not treated (n=27)	9	11	3	4
No treated (n=40)	15	15	8	2
Response on treatment (n=54) [†]				
Oestrogen $\pm$ progestogen (n=24)	13	10	1	0
Clomiphene citrate (n=19)	7	4	7	1 [‡]
Human pituitary gonadotrophin (n=7)	5	1	0	1
Bromocriptine (n=4)	4	0	0	0

* Not related to oestrogen $\pm$ progestogen therapy.

[†] 14 patients received two forms of therapy.

[‡] One patient conceived once on clomiphene and then once spontaneously.

when they fell spontaneously ovulation could often be successfully induced with clomiphene or human pituitary gonadotrophin if anovulation persisted. The fluctuating pattern of gonadotrophin secretion that seems to occur in some potentially fertile women is illustrated in the figure, which shows a patient who conceived triplets after at least four years with intermittently raised gonadotrophin concentrations.

Eight pregnancies occurred in six women in this group. One patient conceived twice on gonadotrophin treatment and another once after clomiphene induction and once spontaneously, while the remaining four ovulated and conceived without treatment. Six completed pregnancies were uncomplicated and healthy infants were delivered, suggesting that the risk of fetal loss was not increased in hypergonadotrophic patients who later conceived. Both of the pregnancies currently in progress occurred spontaneously.

Clinical and biochemical parameters of a patient with intermittent raised FSH values monitored sequentially over four years; she eventually spontaneously conceived triplets in May 1980. A urinary pregnanediol value exceeding 2.0 mg/24 h is considered evidence of ovulation. Arrows indicate FSH assays that were not fully titrated so that values were >40 U/l.

Conversion: SI to traditional units—Oestrogens (as oestradiol): 1 nmol/l ≈ 0.272 μg/24 h. Pregnanediol: 1 μmol/24 h ≈ 0.32 μg/24 h.

Discussion

More than one-quarter of the 67 young women in this series resumed normal ovarian function within one to five years of being suspected of being prematurely menopausal on the basis of at least one raised plasma FSH value. Clinical features such as age or mode of presentation did not help to differentiate those with a transient or a permanent increase in FSH concentration, although the two groups differed significantly in mean LH and total oestrogen concentrations.

Laparoscopy permitted diagnosis of the six patients with streak gonads but was also associated with the only definitely inaccurate ovarian biopsy result, a finding noted by others.¹⁵⁻²¹ The three patients who remained anovulatory despite positive biopsies presumably represent cases of the "resistant ovary syndrome."¹¹ Open biopsy at laparotomy to obtain a representative sample of ovarian tissue is therefore justified in patients with premature hypergonadotrophism who are anxious to conceive, since the prognostic advantages outweigh the risks²² of peritubal adhesion formation. Chromosomal abnormality, antineoplastic drug therapy, and autoimmune disorders are recognised causes of premature ovarian failure and were present in a few of our patients. Antibody studies and karyotyping were not performed in all subjects, however.

Most of our patients could be deemed to have "constitutionally early menopause" when no further ovulation followed or "gonadotrophin resistant ovary syndrome" in the responsive group. It has been proposed that the latter disorder is due to an autoimmune-induced defect of FSH-receptor protein²³ since the primordial follicles remaining in the ovary are resistant to both endogenous and exogenous gonadotrophins. In the absence of a coexistent autoimmune condition, in particular Addison's disease,²⁴ the evidence for an immunological basis for premature menopause is scanty²⁵ and not all reported pregnancies after an increase in FSH values in the menopausal range can be attributed to this syndrome.¹⁷⁻²⁶ Gradually increasing follicular resistance with episodic hypergonadotrophism alternating with ovulatory cycles is not uncommon during the normal menopausal transition⁸⁻⁹ (also J B Brown in lecture at 21st Annual Meeting of Endocrine Society of Australia, 1978) and may be due to a progressive reduction with age of follicular inhibin, which is thought to have a specific negative feedback effect on FSH.²⁷ We have recently observed two patients with ovulatory cycles

(one of whom conceived) with "menopausal" FSH values in the early cycle which then fell before the mid-cycle ovulatory surge. Many of our ovulatory patients were therefore probably behaving as if in the normal perimenopausal transition, so that a representative ovarian biopsy on any of them would have shown residual primordial follicles.²⁸

As long as plasma FSH levels remain raised no specific mode of treatment for the menstrual disturbance is justified, other than oestrogen replacement for menopausal symptoms. No apparent improvement is achieved by oestrogen treatment since although the raised FSH and LH values fall during treatment, they rise rapidly again to pretreatment levels when oestrogens are withdrawn. Apart from being ineffective in restoring ovarian function, oestrogen administration obscures the fact that the FSH and LH values have returned to normal spontaneously, as they will do in at least a quarter of patients.

Following several reports of conception on or just after oestrogen treatment when a diagnosis of premature ovarian failure had been made¹⁴⁻¹⁵ it has been suggested that exogenous oestrogen may increase follicular sensitivity to endogenous gonadotrophin.¹⁶ We consider that oestrogen therapy is more likely to have coincided in these cases with a spontaneous reduction in follicular gonadotrophin resistance, leading to a secondary fall in FSH concentrations and resumption of ovulation. This hypothesis is supported by the finding that in our series conception was commonest in women receiving no treatment (table III) and that only one patient ovulated and none conceived on or soon after oestrogen treatment. Oestrogen-treated and untreated patients in our study were unselected since oestrogens were prescribed only if FSH concentrations remained raised and if symptoms were troublesome. If FSH concentrations returned to normal subsequently but anovulation persisted, however, both clomiphene and gonadotrophin therapy could successfully induce ovulation.

In conclusion, we suggest that the possibility of subsequent ovulation and conception is not as remote in younger patients with raised FSH values associated with menstrual disturbance as has hitherto been assumed and that once it occurs pregnancy is usually uncomplicated. Not all our patients who subsequently ovulated wished to conceive, so that contraceptive advice may be necessary if spontaneous cycles resume.²⁹ Open ovarian biopsy improves the accuracy of prognosis; if it confirms the presence of some primordial follicles continued follow-up with at least twice-yearly gonadotrophin estimations is worth while, particularly in women desirous of further pregnancy.

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References

- Ross GT, Cargille CM, Lipsett MB, *et al*. Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles. *Recent Prog Horm Res* 1970;**26**:1-62.
- Korenman S, Sherman BM. Further studies of gonadotrophin and estradiol secretion during the preovulatory phase of the human menstrual cycle. *J Clin Endocrinol Metab* 1973;**36**:1205-9.
- Pepperell RJ, Burger HG, De Kretser DM, Rennie GC. Plasma gonadotrophin levels in ovulatory and anovulatory patients. *Br J Obstet Gynaecol* 1976;**83**:68-76.
- Goldenberg RC, Grodin JM, Rodbard D, Ross GT. Gonadotrophins in women with amenorrhoea. *Am J Obstet Gynecol* 1973;**116**:1003-12.
- Burch PR, Gunz FW. The distribution of the menopausal age in New Zealand. *N Z Med J* 1967;**66**:6-10.
- Francis WJ. Reproduction at menarche and menopause in women. *J Reprod Fertil* 1970;**12**, suppl:89-98.
- Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol and progesterone concentrations during menstrual cycles of older women. *J Clin Endocrinol Metab* 1976;**42**:629-36.

- ⁸ Metcalf MG, Donald RA. Fluctuating ovarian function in a perimenopausal woman. *N Z Med J* 1979;**89**:45-7.
- ⁹ Jacobs HS, Knuth UA, Hull MG, Franks S. Post-pill amenorrhoea—cause or coincidence? *Br Med J* 1977;iii:940-2.
- ¹⁰ Pepperell RJ. Clinical investigation and assessment of amenorrhoea. *Proceedings of 6th Asia Oceania Congress in Endocrinology*. Singapore: Endocrine and Metabolic Society of Singapore, 1978:389-92.
- ¹¹ Jones GS, De Moraes-Ruehsen M. A new syndrome of amenorrhoea in association with hyper-gonadotrophism and apparently normal ovarian follicular apparatus. *Am J Obstet Gynecol* 1969;**104**:597-600.
- ¹² Kim MH. "Gonadotrophin-resistant ovaries" syndrome in association with secondary amenorrhoea. *Am J Obstet Gynecol* 1974;**120**:257-63.
- ¹³ Dewhurst CJ, De Koos ED, Ferreria HE. The resistant ovary syndrome. *Br J Obstet Gynaecol* 1975;**82**:341-5.
- ¹⁴ Shapiro AG, Rubin A. Spontaneous pregnancy in association with hyper-gonadotrophic ovarian failure. *Fertil Steril* 1977;**28**:500-1.
- ¹⁵ Shangold MM, Turksoy RN, Bashford RA, Hammond CB. Pregnancy following "the insensitive ovary syndrome." *Fertil Steril* 1977;**28**:1179-81.
- ¹⁶ Szlachter BN, Nachtigall LE, Epstein J, Young BK, Weiss G. Premature menopause: a reversible entity? *Obstet Gynecol* 1978;**54**:396-8.
- ¹⁷ Wright CS, Jacobs HS. Spontaneous pregnancy in a patient with hypergonadotrophic ovarian failure. *Br J Obstet Gynaecol* 1979;**86**:389-92.
- ¹⁸ Brown JB, MacLeod SC, MacNaughtan C, Smith MA, Smyth B. A rapid method for estimating oestrogens in urine using a semi-automatic extractor. *J Endocrinol* 1968;**42**:5-15.
- ¹⁹ Barrett SA, Brown JB. An evaluation of the method of Cox for the rapid analysis of pregnanediol in urine by gas liquid chromatography. *J Endocrinol* 1970;**47**:471-80.
- ²⁰ Pepperell RJ, Brown JB, Evans JH, Rennie GC, Burger HG. The investigation of ovarian function by measurement of urinary oestrogen and pregnanediol excretion. *Br J Obstet Gynaecol* 1975;**82**:321-2.
- ²¹ Sutton C. The limitations of laparoscopic ovarian biopsy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1974;**81**:317-20.
- ²² Logan Edwards R, Duignan NM, Rudd BT, Holder G, Butt WR. In: *Diagnosis and treatment of ovarian neoplastic alterations*. Amsterdam: Excerpta Medica, 1974:36. (Excerpta Medica International Congress Series No 364).
- ²³ Jones GS. Comment: the resistant ovary syndrome. *Obstet Gynec Surv* 1975;**30**:700.
- ²⁴ Irvine WJ, Chan MM, Scarth L, et al. Immunological aspects of premature ovarian failure associated with idiopathic Addison's disease. *Lancet* 1968; ii:883-7.
- ²⁵ Coulam CR, Ryan RJ. Premature menopause: etiology. *Am J Obstet Gynecol* 1979;**133**:639-43.
- ²⁶ Thomas PR, Winstanley D, Peckham MD, Austin DE, Murray MA, Jacobs HS. Reproductive and endocrine function in patients with Hodgkins disease: effects of oophorectomy and irradiation. *Br J Cancer* 1976;**33**:226-31.
- ²⁷ Sherman BM, Korenman SG. Hormonal characteristics of the human menstrual cycle throughout reproductive life. *J Clin Invest* 1975;**55**:699-706.
- ²⁸ Reyes FI, Winter JS, Faiman C. Pituitary ovarian relationships preceding the menopause. *Am J Obstet Gynecol* 1977;**129**:557-64.
- ²⁹ Anonymous: Have I stopped ovulating yet? *Lancet* 1979;ii:477-8.

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Management of female breast disease by Southampton general practitioners

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Summary and conclusions

One hundred and two Southampton general practitioners were interviewed about female breast disease. There was agreement about clinical management and the need to both teach and promote breast self-examination. The general practitioners, however, were divided as to whether any breast screening facilities were needed in Southampton. Records kept by the general practitioners of women seen with breast symptoms showed that one-quarter of all new episodes were referred to hospital at the first visit. That the general practitioners considered early diagnosis to be important was made evident from a number of the results. This attitude is encouraging in view of the evidence showing that long-term survival may be greater when delays are shorter.

Introduction

Few detailed studies in Britain have looked at general practitioners' views on the management of breast disease, although

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this has been done with a sample of Australian doctors.¹ In a study of the incidence and management of female breast disease in one practice in Birmingham five general practitioners were interviewed about their policies for managing patients with breast symptoms, but only a brief account of their views was reported.² One of the aims of the present study, which constitutes one part of a broader research project evaluating health education in breast cancer, was to investigate general practitioners' views on managing female breast disease. A further aim was to determine the proportion of women with breast symptoms who were referred to hospital and the proportion dealt with by general practitioners alone.

Methods

All 112 NHS general practitioners and trainees practising in the City of Southampton were sent a letter explaining the purpose of the study and asking them to participate. This was followed within a few days by a telephone call to the surgery to arrange an interview. All interviews were conducted by SN between January and March 1980. The semi-structured questionnaire* contained items about breast disease including the clinical management, cancer survival rates and risk factors, breast self-examination and other screening methods, and health education.

At the end of the interview each doctor was asked to record, for four weeks, all women seen with breast symptoms. A booklet was provided for this purpose which, when completed, provided information about the age and presenting symptoms of each woman together with the action taken by the general practitioner.

*Copies of the questionnaire are available from SN.