Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II

Brian Harris, Lisetta Lovett, Robert G Newcombe, Graham F Read, Richard Walker, Diana Riad-Fahmy

Abstract

***Objectives*—To define relation between mood and concentrations of progesterone and cortisol during perinatal period to test hypothesis that rapid physiological withdrawal of steroid hormones after delivery is associated with depression.**

***Design*—Prospective study of primiparous women from two weeks before expected date of delivery to 35 days postpartum.**

***Setting*—Antenatal clinic in university hospital, obstetric inpatient unit, patients' homes.**

***Subjects*—120 of 156 primiparous women interviewed. Remainder excluded because of major marital, socioeconomic, or medical problems or because caesarean section required.**

***Main outcome measures*—Concentrations of progesterone and cortisol in saliva samples; women's moods assessed by various scores for depression.**

***Results*—Changes in salivary progesterone and cortisol concentrations were similar to those already characterised for plasma. Peak mean score for maternity blues (5·3 on Stein scale) was on day five postpartum ($P<0·02$ compared with mean scores on other postpartum days). High postpartum scores for maternity blues were associated with high antenatal progesterone concentrations on day before delivery ($P<0·05$), with high rate of rise of antenatal progesterone concentrations ($P<0·05$), with decreasing progesterone concentrations from day of delivery to day of peak blues score ($P\geq0·01$), and with low progesterone concentrations on day of peak blues score ($P<0·01$). Seventy eight women were designated as having maternity blues (peak score ≥8 on Stein scale) while 39 had no blues. Women with blues had significantly higher antenatal progesterone concentrations and lower postnatal concentrations than women without blues (geometric mean progesterone concentrations: one day before delivery 3860 pmol/l *v* 3210 pmol/l respectively, $P=0·03$; ten days postpartum 88 pmol/l *v* 114 pmol/l, $P=0·048$). Cortisol concentrations were not significantly associated with mood.**

***Conclusion*—Maternal mood in the days immediately after delivery is related to withdrawal of naturally occurring progesterone.**

Department of Psychological Medicine, University of Wales College of Medicine, Cardiff CF6 2YA
Brian Harris, *senior lecturer*

Department of Medical Computing and Statistics, University of Wales College of Medicine
Robert G Newcombe, *senior lecturer*

Department of Psychiatry, Leighton Hospital, Crewe CW1 4QJ
Lisetta Lovett, *consultant psychiatrist*

Steroid Assay Laboratory, Tenovus Institute, University Hospital of Wales, Cardiff CF4 4XW
Graham F Read, *principal biochemist*
Richard Walker, *research biochemist*
Diana Riad-Fahmy, *consultant biochemist*

Correspondence to:
Dr Harris.

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Introduction

Maternity blues refers to the tearfulness, irritability, hypochondriasis, sleeplessness, impairment of concentration, and headache that occurs in the 10 days or so postpartum.[1,2] A peak in symptoms occurs around the fourth to fifth day after delivery,[3,4] coinciding with maximal hormonal changes.[5] These include falling concentrations of progesterone, oestradiol, and cortisol and rising prolactin concentrations. Such hormonal changes may have a causal relation to blues. Changes in concentrations of progesterone and its derivatives are of particular interest because of its well documented anaesthetic action.[6-8] During pregnancy, progesterone concentrations slowly rise to a maximum at term, when they are several hundred times higher than normal.[5] After delivery and the withdrawal of the placenta there is a precipitate drop in progesterone concentration. It is therefore possible that the symptoms of maternity blues are related to progesterone withdrawal. Cortisol concentrations also rise during pregnancy to several times their normal values. They rise further during the stress of labour and then slowly return to normal within 15 days of delivery.

Monitoring concurrent changes in mood and hormone concentrations has been difficult, however, because frequent venepuncture is unacceptable and because total hormone concentrations are usually measured[9] whereas only a small fraction of the hormone is free and biologically active.[10] Over the past 15 years saliva sampling has been developed as an alternative to blood sampling for measuring cortisol and progesterone concentrations by means of sensitive radioimmunoassay techniques.[11] Concentrations in saliva accurately reflect plasma concentrations of free hormone even under conditions of altered saliva flow.[12,13] It has also been shown that concentrations of steroid hormones in the cerebrospinal fluid are closely correlated with plasma concentrations of unbound hormone[14] so that salivary concentrations are likely to accurately reflect concentrations in cerebrospinal fluid.

The purpose of the present study was to test the hypothesis that postnatal depressed mood is related to the withdrawal of progesterone or cortisol after delivery.

Subjects and methods

Primiparous women, who were booked to remain in hospital for five days after delivery according to the normal obstetric practice in Cardiff, underwent an initial screening interview by two research nurses two weeks before the expected date of delivery. The study design was similar to that of Nott *et al.*[9] Women were given an informal explanation in the antenatal clinic some weeks before entry into the study. They were also given an information sheet and were told that they would be paid £10 on completing the study.

The screening process and entry were completed at the routine antenatal clinic. Only eight women refused to be involved in the study, and 156 women were interviewed by one of the research nurses. The women were asked to discuss their relationship with their husband or partner and then to rate it on a simple scale as excellent, very good, good, fair, or poor. Women who rated their relationship as fair or poor were excluded from the study. Similarly, those with physical illness that required continuing treatment or who had had admissions to hospital during their pregnancies were excluded. Women who were homeless or in considerable financial difficulties were also excluded from the study.

Altogether, 26 women were excluded because of substantial marital, health, or socioeconomic problems. The resultant sample of 130 women was about 5% of the total number of primiparous women who delivered at the hospital during the two years of the study. This sample size was calculated to yield a

power of about 80% to detect a correlation of 0·25 with a 5% level hypothesis test.

ASSESSMENT OF MOOD

At the initial interview the women gave their full informed consent for participation and completed questionnaires for self rating of mood—based on the Edinburgh postnatal depression scale,[15] the Stein scale for maternity blues,[16] and the Beck depression rating inventory.[17] After delivery the women completed a questionnaire based on the Stein scale each evening for 10 days. At 35-40 days after delivery each mother was assessed at a home visit (to be reported elsewhere) by an experienced psychiatrist (BH or LL). A clinical assessment was made using criteria for major depression (*Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised), followed by completion of questionnaires based on the Montgomery and Asberg depression rating scale and the Edinburgh postnatal depression scale. Life events that had occurred during the preceding year were noted on the Paykel life events schedule, and each mother was given a Beck depression rating inventory for later completion and return by post.

MEASUREMENT OF HORMONE CONCENTRATIONS

Saliva sampling—The women were shown how to collect saliva and were asked to take samples at 0800 and 2200 hours daily until delivery; at 0800, 1400, and 2200 hours daily for the next five days; and then again at 0800 and 2200 hours daily until the home visit. Saliva samples and kit were kept in the ice box compartment of a fridge or in a deep freeze.

Blood sampling—Blood samples were collected at the initial screening interview and at one, five, and 35 days after delivery.

Hormone assays—Plasma concentrations of progesterone and oestradiol were measured with commercial radioimmunoassay kits (Coat-A-Count and Double Antibody, Diagnostic Products, Caernarfon), and concentrations of plasma cortisol, salivary cortisol, and salivary progesterone were determined as described previously.[18,19] All 9654 saliva samples (75% compliance) were processed for progesterone. However, only 4862 selected samples were assayed for cortisol: patients were graded according to their scores on the Edinburgh depression scale that they completed at their final psychiatric assessment, and saliva samples were assayed from the 20 highest scoring women, the 20 lowest scoring, and the 20 scoring nearest the middle of the range.

STATISTICAL METHODS

Progesterone and cortisol concentrations were log transformed for analyses because of gross positive skewness. All comparisons between women who developed maternity blues and whose who did not are thus ratios. Decrements in log concentrations of progesterone and cortisol were calculated by comparing postnatal values with an average of prenatal values from seven to two days before delivery. To measure associations betwen prenatal progesterone concentrations and postnatal blues, each woman was assigned log progesterone concentrations for days 14 and 1 before delivery and a gradient of increasing progesterone log concentration from day 14 to day 1 based on an individual regression model. The slope was calculated only if based on 10 or more readings. The log concentration for day 1 before delivery was taken from the regression equation if there were 10 or more readings, otherwise a simple average of available readings was used. The log concentration for day 14 was fitted only if 10 or more readings as early as this were available. Because of the nature of the Stein scale, and notwithstanding the use of log transformation, associations were measured by the Spearman rank correlation.

Results

None of the 130 women recruited into the study delivered a stillborn or severely handicapped child, but only 120 had vaginal deliveries—71 were spontaneous and 49 were induced. The 10 women who required a caesarean section were excluded from the study. The remaining women were aged 18-40 with a mean (SD) of 26·4 (4·4) years. At the final interview 57 women were breast feeding and 61 were bottle feeding (feeding status was not recorded for two women). Nine of those breast feeding and 15 of those bottle feeding were taking oral contraceptives.

PSYCHOMETRY

Most women experienced some symptoms of blues in the 10 days after delivery: Stein scores ranged from 0 to 24, and 80 (67%) of the women scored 8 or above (the cut off point for having maternity blues suggested by Stein) on one or more days. The trimmed mean score (based on the middle 90% of values) fell from 5·0 on day 1 postpartum to 3·9 on day 3, rose to 5·3 on day 5, and fell to 3·7 on day 10 (Friedman test, $P<0·02$; two way analysis of variance on normal scores, $P<0·001$).

Individual subjects' profiles of Stein scores did not approximate to smooth curves, and there was no clear pattern of the timing of their peak scores. Peak Stein scores were associated with symptoms of antenatal depression (based on antenatal score for Edinburgh postnatal depression scale) (Spearman rank correlation, $r=0·31$, $P<0·001$).

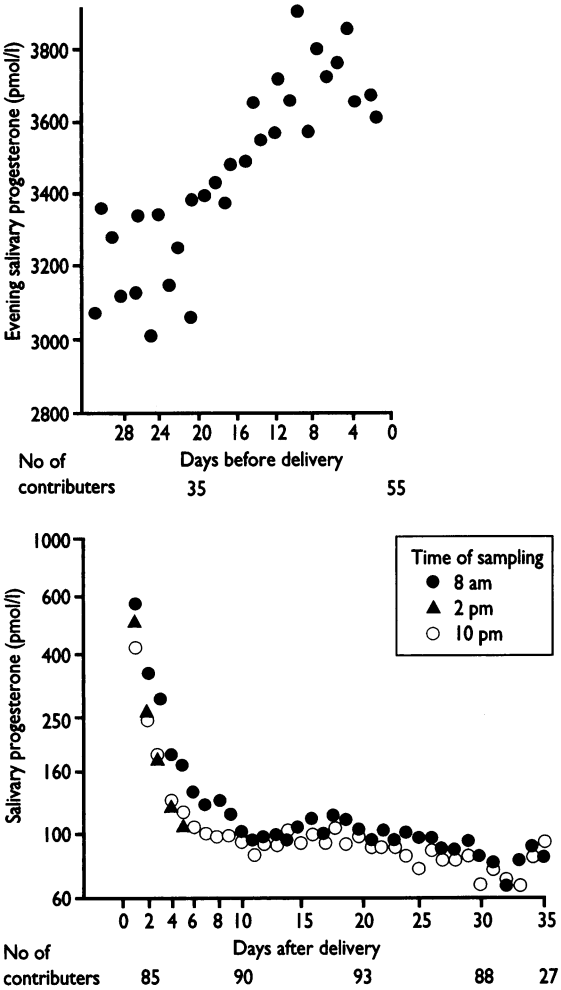

FIG 1—*Salivary progesterone concentrations in women during perinatal period. Statistical analysis of results described by Harris et al*[20]

HORMONE CONCENTRATIONS

Figure 1 shows the changes in salivary concentrations of progesterone during the last two weeks of pregnancy and the first 35 days after delivery. There was no circadian variation in concentration but a continual significant rise before delivery up to a concentration of 3855 pmol/l on the day before delivery (plasma equivalent 694·8 nmol/l). In the first four to five days after delivery the concentration dropped precipitately to typical values of 150 pmol/l by day 5 postpartum and 80 pmol/l by day 10; (plasma equivalents 7·7 nmol/l and 2·7 nmol/l respectively).

Figure 2 shows salivary cortisol concentrations. Evening concentrations rose slowly during the last 30 days of pregnancy with a highly significant rise on the evening before delivery. There was also a slow but significant fall in morning cortisol. Diurnal rhythm was still detectable the day before delivery with morning saliva concentrations of 13·3 nmol/l falling to 5·5 nmol/l by day 15 postpartum (plasma equivalents 530 nmol/l and 200 nmol/l respectively). Of those subjects for whom cortisol concentrations were assayed, 23 had had induced deliveries with artificial rupture of the membranes. There was no significant difference in the profiles of cortisol concentrations for these women compared with those for women who had spontaneous delivery: in both groups concentrations returned to normal by about day 15 postpartum.

Plasma progesterone, oestradiol, and cortisol concentrations in late pregnancy and immediately after delivery were similar to those reported by other workers[5 10 21] (detailed results available from the authors).

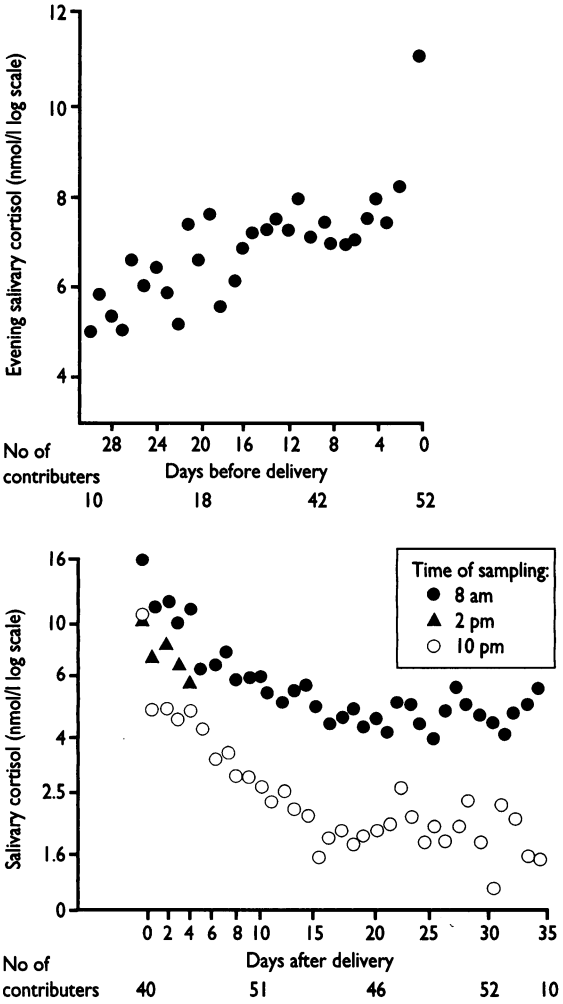

FIG 2—*Salivary cortisol concentrations in women during perinatal period. Statistical analysis of results described by Harris et al*[20]

ASSOCIATIONS OF HORMONE CONCENTRATIONS AND PSYCHOMETRIC SCORES

Table I shows that there were significant positive associations between women's blues scores on early postpartum days and their antenatal morning and evening progesterone concentrations. Also, the steeper the rise in antenatal progesterone concentrations the higher the peak blues score. Table II shows that the greater the postnatal fall in progesterone concentrations (from the average concentration on days 7 to 2 before delivery) the higher the peak Stein score. Of a total of 66 correlations between the morning and evening progesterone concentrations on prenatal days 14 and 1, and the gradients between those days, with the Stein scores on each of the postpartum days, 16 reached the 5% level of significance (table I) whereas only three or four would be expected to occur by chance.

For the whole group there was an inverse association between the blues score on a particular day and the

TABLE I—*Associations (Spearman rank correlations) of prenatal salivary progesterone concentrations with postpartum Stein scores for maternity blues (Stein scale)*

	Concentration one day before delivery				Concentration 14 days before delivery				Gradient of concentration increase (from day 14 to day 1)			
	Morning		Evening		Morning		Evening		Morning		Evening	
	r Value (P value)	No of subjects	r Value (P value)	No of subjects	r Value (P value)	No of subjects	r Value (P value)	No of subjects	r Value (P value)	No of subjects	r Value (P value)	No of subjects
Day 1	0·25 (0·03)	70	0·28 (0·02)	69	0·33 (0·05)	38	0·18 (0·27)	38	0·15 (0·33)	47	0·32 (0·03)	47
Day 2	0·17 (0·08)	105	0·22 (0·02)	104	0·16 (0·23)	60	0·09 (0·47)	61	0·26 (0·03)	74	0·42 (0·001)	73
Day 3	0·17 (0·08)	105	0·22 (0·02)	104	0·30 (0·02)	60	0·29 (0·03)	61	−0·03 (0·83)	74	0·01 (0·91)	73
Day 4	0·22 (0·03)	104	0·29 (0·004)	103	0·24 (0·07)	60	0·21 (0·11)	61	0·03 (0·83)	74	0·05 (0·67)	73
Day 5	0·13 (0·21)	99	0·08 (0·44)	98	0·18 (0·18)	56	0·13 (0·32)	57	0·23 (0·05)	70	0·05 (0·66)	69
Day 6	0·11 (0·26)	99	0·13 (0·19)	98	0·04 (0·78)	57	0·02 (0·86)	58	0·20 (0·10)	71	0·13 (0·28)	70
Day 7	0·07 (0·49)	98	0·06 (0·58)	97	−0·11 (0·42)	56	−0·04 (0·74)	57	0·25 (0·04)	70	0·12 (0·33)	69
Day 8	0·14 (0·16)	97	0·09 (0·40)	96	0·06 (0·68)	55	0·09 (0·52)	56	0·17 (0·14)	69	0·08 (0·50)	68
Day 9	0·00 (0·90)	98	0·02 (0·82)	97	−0·01 (0·97)	56	−0·03 (0·80	57	0·09 (0·43)	70	0·04 (0·70)	69
Day 10	0·02 (0·84)	95	0·03 (0·80)	94	0·14 (0·30)	54	0·16 (0·26)	55	0·02 (0·87)	68	−0·04 (0·75)	67
Peak Stein score (recorded during days 1-10)	0·20 (0·04)	105	0·21 (0·03)	104	0·13 (0·32)	60	0·12 (0·38)	61	0·22 (0·06)	74	0·14 (0·25)	73

progesterone concentration on that day. There was also an inverse association between peak blues score and the drop in progesterone concentration from days 2 to 10 postpartum (table II). Of 50 correlations between the peak Stein score and various prenatal and postnatal progesterone concentrations (including the decrements from prenatal to postnatal days), 10 reached the 5% level of significance and four reached the 1% level or beyond. The Stein score on day 5 postpartum correlated positively with the progesterone concentration on day 4 ($r=0{\cdot}22$, $P=0{\cdot}05$, $n=78$), possibly indicating an association with the fall in progesterone concentration between days 4 and 5 postpartum.

Of the 118 subjects who completed antenatal Stein questionnaires, 78 scored ≥ 8 (the cut off point for maternity blues) at some time after delivery, while the remaining 39 women scored below the cut off point. There was a significant tendency for the antenatal progesterone concentrations to be higher and the postnatal progesterone concentrations to be lower in the group of women with blues compared with those without blues. For example, the geometric mean progesterone concentrations on the morning of the day before delivery were 3860 pmol/l for 68 women with blues and 3210 pmol/l for 36 women without blues, giving an estimated ratio of 1·20 (95% confidence interval 1·02 to 1·42) ($t=1{\cdot}15$, $P=0{\cdot}027$). Also, the geometric means of the ratio of progesterone concentration on day of peak Stein score to the prenatal value were 0·043 for 55 women with blues and 0·072 for 27 women without blues (estimated ratio 0·60 (0·42 to 0·86), $t=2{\cdot}82$, $P=0{\cdot}006$).

Statistical analyses were also applied to saliva cortisol concentrations, but no significant associations emerged (table II). Spearman rank correlations were also calculated for peak Stein scores with plasma hormone concentrations and changes in these across delivery. There were no associations of blues with plasma hormones, neither their mean concentrations at the times of plasma sampling nor the decrements in concentrations from before delivery to day 5 postpartum.

Discussion

The high prevalence of maternity blues and its relative ease of detection has led to many investigations of possible causes. Steroid hormones, body weight, fluid and electrolytes,[22] calcium concentrations,[23] monoamines,[24] tryptophan,[25] and platelet receptors[26] have all been studied for associations with blues. So far as steroid hormones are concerned, there are practical implications: severe blues often progresses into a major depressive episode,[27] and some have advocated treatment with progesterone,[28] assuming that depressed mood is linked to falling progesterone levels.

Our results show that there is a weak but significant association of maternity blues with higher antenatal salivary progesterone concentrations, lower concentrations shortly after delivery, and greater decreases in concentration from antenatal to postnatal values. This was not confirmed with plasma progesterone, possibly because total plasma progesterone concentration (only a small proportion of which is free and biologically active) was measured. A similar negative finding was reported by O'Hara *et al*, who also measured total plasma progesterone.[29] Anderson *et al* showed that, despite the progesterone concentration rising several hundred times in late pregnancy, the amount of free progesterone remains relatively small, being at most 2·8% of the total.[10] The development of blues can therefore be explained at least partly in terms of withdrawal of naturally occurring progesterone.

Animal studies have shown that progesterone has an anaesthetic action, especially the pregnanolone derivatives.[6 8 30] These occur in women and may be more closely related with blues than progesterone itself. This possibility was partly predicted by Selye,[8 31] who suggested the possible use of such hormones as "sleeping pills, tranquillizers," or for "treatment for mental derangements."

Our results are supported by Nott *et al*, who in a much smaller group of 27 women found that the greater the drop in progesterone concentration from antenatal values the more likely were subjects to rate themselves as depressed within 10 days of delivery. So far as cortisol is concerned, our work gives no support to the idea that its withdrawal is important in generating blues.

Further research should concentrate on the possible association of maternity blues with the pregnanolone derivatives of progesterone and on the effect of treatment with progesterone on the severity of blues.

Clinical implications

- Maternity blues are experienced by 30% or more of mothers in the first 10 days after delivery, and severe blues can progress to an episode of major depression
- It has been suggested that maternity blues may be caused by the sudden fall in the mother's circulatory progesterone concentration after delivery
- In this study we found a modest association between scores for maternity blues and changes in progesterone concentrations in the saliva (an accurate measure of circulating free progesterone)
- Development of maternity blues was associated with high antenatal progesterone concentrations, low postnatal concentrations, and a steep fall in concentration after delivery
- It may be possible to attenuate maternity blues by treating mothers with progesterone

TABLE II—*Associations (Spearman rank correlations) of peak Stein scores for maternity blues with postnatal salivary concentrations of progesterone and cortisol and with changes in these concentrations*

	Correlation with peak Stein score					
	Progesterone			Cortisol		
	r Value	No of subjects	P value	r Value	No of subjects	P value
Concentration on days after delivery*:						
Evening value on day 4	−0·22	89	0·04	+0·11	51	0·45
Decrement to morning value on day 5	+0·23	89	0·03	−0·10	49	0·48
Decrement to evening value on day 5	+0·08	80	0·47	+0·07	40	0·67
Morning value on day 5	−0·22	93	0·003	+0·12	54	0·39
Average morning value for days 9-11	−0·24	100	0·02	−0·19	54	0·17
Average evening value for days 9-11	−0·20	96	0·05	+0·01	52	0·95
Morning value on day of peak Stein score	−0·28	86	0·008	−0·19	49	0·18
Decrement to morning value on day of peak Stein score	+0·28	82	0·01	+0·17	46	0·28
Gradient from day 2 to day 10	−0·28	81	0·01	−0·25	39	0·12

*All changes relative to an average of log concentrations for each subject on days 7 to 2 before delivery.

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Audit of elderly people's eye problems and non-attendance at hospital eye service

Jonathan G Hillman

Medical Centre, Bridlington YO16 4LZ
Jonathan G Hillman, *general practitioner*

Correspondence to:
Dr Hillman.

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Because eye disease is common in elderly people[1] and the number of people aged ≥80 in Britain is increasing,[2] outpatient referrals to the hospital eye service will probably rise. Many studies have discussed the reasons why people do not keep their outpatient appointments and ways in which non-attendance could be reduced. Few have given details of the morbidity that arises in patients who have not kept appointments.[3] Could general practitioners have an important influence on non-attendance?

Patients, methods, and results

A manual audit covering September 1991 to June 1992 was made of all records of patients aged ≥75 in a general practice with four partners and 6314 patients. The records were extracted, and notes were made of the number of patients under the care of the hospital eye service; the diagnosis made by the consultant ophthalmologist in each case; the number of patients registered as blind or partially sighted; and the number of patients who had not kept follow up appointments with the hospital eye service in the preceding 10 years. An attempt was then made to contact all those patients who had not kept appointments. When possible, reasons for their non-attendance were obtained, and those who agreed were sent an appointment to attend the hospital eye service. One year later the records of the non-attenders were analysed again to determine the outcome of this intervention.

Of the 838 patients aged ≥75, 69 were registered as partially sighted and 22 as blind. Altogether 199 patients were attending the hospital eye service. Forty two were under review because they had glaucoma and 72 because of cataracts; 59 had macular degeneration; and 26 had other eye disorders. A total of 49 patients had not kept follow up appointments after having attended at least once. The table shows the results of the repeat analysis of the non-attenders 12 months later. Of the 14 patients who had been given a further appointment, 10 had treatable eye conditions: six had cataracts extracted and four had glaucoma. One of the patients with glaucoma was registered as partially sighted.

Eye disease in 49 elderly patients lost to follow up with hospital eye service

Disorder	Agreed to reattend (n=14)	Unwell or refused to reattend (n=21)	Died during audit (n=14)
Cataracts	6	6	3
Macular degeneration	3	11	5
Glaucoma	4	1	3
Other disorders	1	3	3

Twenty two of the non-attenders gave reasons for not keeping their appointments: 10 had not received an appointment; six had not understood that further attendance was necessary; and six had found their experience as an outpatient upsetting and did not wish to return. Ten non-attenders gave no reason, three could not be interviewed because of dementia, and 14 had died. No one admitted to having forgotten their appointment.

Comment

We found that a quarter of the elderly people in our practice were attending the hospital eye service. If this proportion is representative of the situation in the rest of Britain it implies a heavy workload on outpatient services in eye departments, which is reflected in the long waiting lists for this specialty. The audit also showed that a quarter of the patients had been lost to follow up at the hospital's eye department. This was attributed partly to a flaw in communication in the outpatient department, which has now been corrected through the introduction of full computerisation, and partly to human frailty, which intensifies with age. The findings emphasise, however, that staff must give more time to, and be more patient with, elderly people to ensure that instructions are fully understood. Appropriate leaflets printed in large type may also help.

The patients who were "retrieved" had suffered appreciable morbidity. If the outpatient department notified general practices of non-attenders the general practitioners or their staff could follow up these patients, especially those with progressive disease.

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