

## PAPERS AND SHORT REPORTS

## Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism

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### Abstract

Polycystic ovaries were defined with ultrasound imaging in a series of 173 women who presented to a gynaecological endocrine clinic with anovulation or hirsutism. Polycystic ovaries were found in 26% of women with amenorrhoea, 87% with oligomenorrhoea, and 92% with idiopathic hirsutism—that is, hirsutism but with regular menstrual cycles. Fewer than half the anovulatory patients with polycystic ovaries were hirsute, but in 93% of cases there was at least one endocrine abnormality to support the diagnosis of polycystic ovaries—that is, raised serum concentrations of luteinising hormone, raised luteinising hormone: follicle stimulating hormone ratio, or raised serum concentrations of testosterone or androstenedione. This study shows that polycystic ovaries, as defined by pelvic ultrasound, are very common in anovulatory women (57% of cases) and are not necessarily associated with hirsutism or a raised serum luteinising hormone concentration. Most women with hirsutism and regular menses have polycystic ovaries so that the term “idiopathic” hirsutism no longer seems appropriate.

### Introduction

The polycystic ovary syndrome is commonly associated with failure of ovulation, but the prevalence of polycystic ovaries in women with anovulation is difficult to assess. This is partly because diagnosis usually depends on the finding of typical clinical and biochemical features associated with polycystic ovaries rather than morphological assessment of the ovary.<sup>1-4</sup> The precise diagnosis of polycystic ovaries, however, depends on histological findings of multiple follicular cysts and increased stroma in ovaries that are

usually, but not always, enlarged.<sup>5</sup> These are features that can be identified using high resolution ultrasonography of the ovaries.<sup>6,8</sup> We therefore used ultrasound to identify the presence of polycystic ovaries in a large series of women who presented to the gynaecological endocrine clinic with amenorrhoea or oligomenorrhoea. We also scanned the ovaries of women with hirsutism and regular menstrual cycles—that is, idiopathic hirsutism.

### Patients and methods

This series included 173 consecutive patients with amenorrhoea, oligomenorrhoea, or hirsutism presenting to the gynaecological endocrine clinic. Hirsutism was described as mild (Ferriman-Gallwey score 6-9), moderate (10-14), or severe (15+).<sup>9</sup> The patients studied included 73 with amenorrhoea (5 primary, 68 secondary), 75 with oligomenorrhoea and anovulation, and 25 who had hirsutism (11 mild, 12 moderate, and two severe) but regular periods. The control group comprised 21 women with normal ovaries on ultrasonography and regular ovulatory cycles, studied during the early to mid-follicular phase of the menstrual cycle (days 1-9). The mean age of the control group was similar to that of the patients. None of the controls had hirsutism or acne. Ovulation was confirmed by measurements of serum progesterone in the luteal phase. Pelvic ultrasonography was performed as previously described.<sup>8</sup> The ovary was defined as being polycystic if there were multiple cysts (10 or more) 2-8 mm in diameter arranged either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma (or both, as in figure 1).<sup>6</sup> The ovaries were usually enlarged.<sup>8</sup>

Measurements of serum concentrations of luteinising hormone, follicle stimulating hormone, prolactin, testosterone, and androstenedione were made by radioimmunoassay as previously described.<sup>8,10</sup> In some cases hormone measurements (for example, for androstenedione) were made in subsets of patients rather than in the whole group (see table III), but these subsets were found to be representative of the groups in terms of clinical, ultrasound, and other biochemical findings. Comparisons between groups were made using Student's *t* test. Because the distribution of luteinising hormone results was found to be skewed, a logarithmic transformation of these data was made before comparison of mean luteinising hormone values.

### Results

The underlying diagnoses in the 73 women with amenorrhoea were based on clinical, ultrasound, and biochemical criteria and are summarised in table I. Ten women (14%) had primary ovarian failure and 8 (11%) had hyperprolactinaemia (serum prolactin concentration >1000 nmol/l (25 µg/l)

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but without evidence of polycystic ovaries. Twenty eight (38%) women had amenorrhoea related to loss of weight and of these, 22 appeared to have typical multifollicular ovaries on ultrasonography, a pattern that is quite distinct from that in polycystic ovaries.<sup>8</sup> A further six patients had hypogonadotrophic amenorrhoea (normal or low gonadotrophin concentrations associated with oestrogen deficiency). In one of these cases it was related to a depressive illness, but the cause in the other five was unclear. Polycystic ovaries were found in 19 women (26%), but only six of these had hirsutism or acne. Interestingly, three women in the group with polycystic ovaries were also underweight (body mass index <19.1 kg/m<sup>2</sup>) but had a polycystic rather than a multifollicular pattern on ultrasonography.

TABLE I—Diagnoses and classification of 173 women with amenorrhoea, oligomenorrhoea, and idiopathic hirsutism

Diagnosis	No (%)
<b>Women with amenorrhoea (n=73)</b>	
Primary ovarian failure	10 (14)
Hyperprolactinaemia	8 (11)
Related to loss of weight	28 (38)
Hypogonadotrophic hypogonadism (not related to weight loss)	6 (8)
Genital tract abnormality	2 (3)
Polycystic ovaries	19 (26)
<b>Women with oligomenorrhoea (n=75)</b>	
Hyperprolactinaemia	1 (1)
Obese (no polycystic ovaries)	3 (4)
Perimenopausal	2 (3)
Recovered weight loss	1 (1)
Unknown	3 (4)
Polycystic ovaries	65 (87)
<b>Women with idiopathic hirsutism (n=25)</b>	
Polycystic ovaries	23 (92)
Normal ovaries	2 (8)

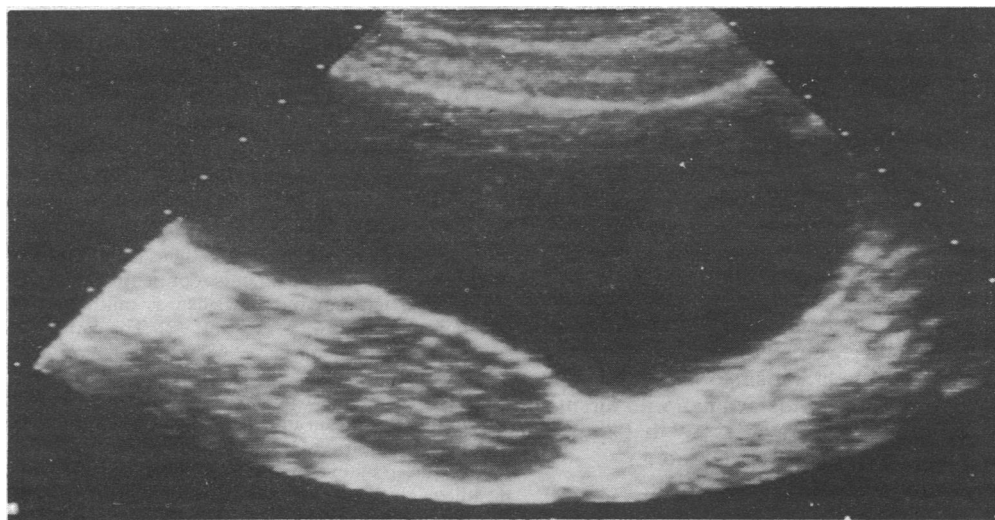


FIG 1—Ultrasound appearance of polycystic ovary. Ovary is enlarged (white dots at the edge of image are 1 cm markers) and contains multiple cysts 2-5 mm in diameter, arranged peripherally and scattered throughout a dense core of echogenic stroma.

Polycystic ovaries were the most common diagnosis in women with oligomenorrhoea, occurring in 65 of 75 women (87%) (table I). Thirty six patients (55%) with polycystic ovaries had hirsutism or acne, or both. Of the 31 women with hirsutism, it was mild in 12, moderate in 14, and severe in five.

Polycystic ovaries were found in 23 of 25 women with hirsutism and regular menses (idiopathic hirsutism) (table I). In 10 of these 23 women hirsutism was classified as mild, in 12 moderate, and in one severe. If the scan was performed in the late follicular or luteal phase of the cycle it was possible to define a dominant follicle or a corpus luteum on ultrasonography despite the polycystic appearance (fig 2). Evidence of ovulation (corpus luteum on ultrasonography or raised progesterone concentrations) was established in 16 of 23 women. In the other seven investigations were performed only in the follicular phase.

Table II shows the mean serum luteinising hormone and follicle stimulating hormone concentrations in the various groups of women with amenorrhoea. Serum luteinising hormone concentrations in amenorrhoeic

TABLE II—Mean (range) concentrations of luteinising and follicle stimulating hormones in four groups of women with amenorrhoea; women with primary ovarian failure (all luteinising hormone values >50 U/l, follicle stimulating hormone >20 U/l) excluded

Diagnosis	No of women	Luteinising hormone (U/l)	Follicle stimulating hormone (U/l)
Polycystic ovaries	19	14.5 (4.0-24)*	4.1 (1.2-8.2)
Hyperprolactinaemia	8	7.3 (4.3-11)	5.0 (3.1-7.7)
Weight loss	23	6.2 (1.7-14)	3.1 (0.7-7.6)†
Hypogonadotrophic hypogonadism	5	4.5 (2.0-6.9)	3.6 (1.0-6.7)
Normal (follicular phase)	16	6.1 (2.5-14)	4.1 (1.3-6.9)

The mean luteinising hormone values were compared after logarithmic transformation of the data (see text).

\*Luteinising hormone concentrations are significantly higher than in the normal follicular phase in women with polycystic ovaries ( $p < 0.001$ , Student's *t* test).

†Follicle stimulating hormone concentrations are normal in polycystic ovaries but reduced ( $p < 0.02$ ) in amenorrhoea related to loss of weight.

patients with polycystic ovaries were significantly greater than those in either normal subjects or other groups of women with amenorrhoea. Half of the women with polycystic ovaries, however, had normal luteinising hormone concentrations (fig 3). The mean serum concentrations of testosterone and androstenedione were greater than normal (table III), but in only 10 of 19 women was the testosterone concentration higher than the upper limit of the normal range for our laboratory (3 nmol/l (865 ng/l)). Only four of 19 women (21%) with polycystic ovaries and amenorrhoea had no hirsutism or acne, normal luteinising hormone concentrations or luteinising hormone: follicle stimulating hormone ratio, and normal serum concentrations of testosterone and androstenedione. Three of these four women who had no clinical or biochemical features of polycystic ovaries were the underweight patients referred to above.

Like the women with amenorrhoea, those with polycystic ovaries and oligomenorrhoea had raised mean gonadotrophin and androgen concentrations (table III, fig 3). Forty of 60 women in whom gonadotrophin concentrations were measured had a raised serum concentration of luteinising hormone or luteinising hormone:follicle stimulating hormone ratio, or both. Serum concentrations of testosterone were above normal in 35 out of 62 (56%) women and androstenedione concentrations were greater than normal in 23 out of 38 (60%). Only two women of the 65 had no clinical or biochemical evidence of the polycystic ovary syndrome—that is, they were non-hirsute and had normal gonadotrophin and androgen concentrations; one of these patients was appreciably underweight.

Luteinising hormone concentrations, the luteinising hormone:follicle stimulating hormone ratio, and testosterone concentrations were usually within the normal range in women with polycystic ovaries and idiopathic hirsutism (fig 3, table III), but the mean serum luteinising hormone and testosterone concentrations were significantly greater than in normal women.

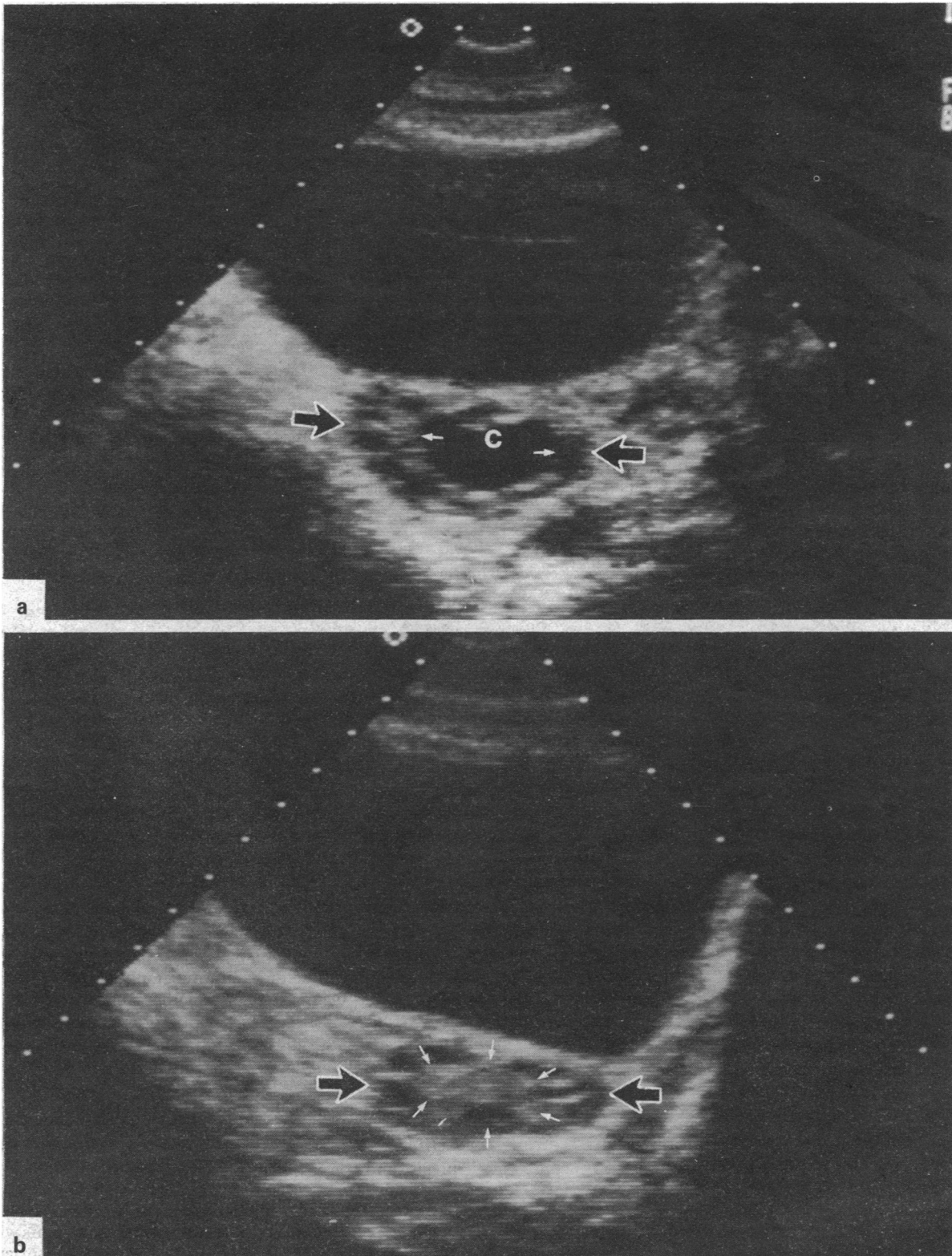


FIG 2—Ultrasound appearance of ovary in women with polycystic ovaries but ovulatory cycles. Fig 2 a shows typical polycystic pattern with a preovulatory follicle (arrowed) containing a clearly visible cumulus oophorus (c). Fig 2 b shows a corpus luteum (arrowed).

### Discussion

Our findings show that polycystic ovaries, as defined by pelvic ultrasound, are often found in anovulatory women and those with idiopathic hirsutism. In this series of patients polycystic ovaries were the most common diagnosis in women with oligomenorrhoea or idiopathic hirsutism and the second most common diagnosis in women presenting with amenorrhoea. An important feature in the

presentation of polycystic ovaries in anovulatory women was that only half of the patients in this series were hirsute (compared with 745 (69%) of 1079 patients with established polycystic ovaries at laparotomy described by Goldzieher and Green<sup>11</sup>). The inter-relationship of the presenting features of our patients with an ultrasound diagnosis of polycystic ovaries is shown in figure 4. Even in the absence of hirsutism most patients with ultrasound evidence of polycystic ovaries had at least one biochemical abnormality

suggestive of the polycystic ovary syndrome, so that although serum luteinising hormone concentrations (or luteinising hormone: follicle stimulating hormone ratio) were normal in about half the cases, only 4 (21%) women with polycystic ovaries and amenorrhoea and only 2 (3%) women with polycystic ovaries and oligomenorrhoea were non-hirsute and had normal serum concentrations of gonadotrophins and androgens.

It is notable that four of the six anovulatory women with polycystic ovaries who had normal serum concentrations of both luteinising hormone and androgens were underweight. Characteristically women with amenorrhoea related to loss of weight have normal serum concentrations of luteinising hormone and testosterone and usually a different pattern of multiple ovarian cysts from that in polycystic ovaries.<sup>8</sup> We suggest that in these few cases the primary cause of the menstrual disturbance was weight related hypothalamic disorder of gonadotrophin secretion rather than the polycystic ovaries themselves.

Our data suggest that idiopathic hirsutism is a manifestation of the polycystic ovary syndrome. Most of these women had ovulatory cycles, and it was therefore not surprising to find that few of these women had raised concentrations of luteinising hormone or a raised luteinising hormone: follicle stimulating hormone ratio. These data are compatible with the findings of Goldzieher and Green, who

found that a corpus luteum was present at laparotomy in 22% of women with established polycystic ovaries.<sup>11</sup>

Thus the clinical and biochemical features of the patients in whom we have diagnosed polycystic ovaries support the specificity of the ultrasound findings. Few of these patients underwent

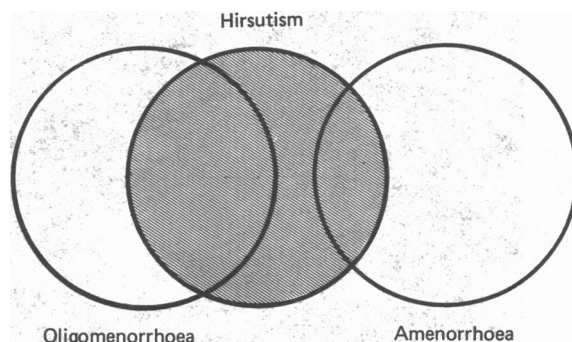


FIG 4—Diagrammatic representation of clinical features of women with ultrasound diagnosis of polycystic ovaries.

TABLE III—Mean serum gonadotrophin and androgen concentrations (range) (No of women) in women with polycystic ovaries compared with those in normal women in the follicular phase of the cycle

	Luteinising hormone (U/l)	Follicle stimulating hormone	Testosterone (nmol/l)	Androstenedione (nmol/l)
Polycystic ovaries				
Amenorrhoea	14.5 (4.0-24) (19)*	4.1 (1.2-8.2) (19)	3.05 (1.7-6.2) (19)*	9.34 (4.4-15) (10)*
Oligomenorrhoea	15.6 (3.7-42) (60)*	4.2 (0.5-7.5) (60)	3.25 (1.3-7.0) (62)*	10.5 (3.7-17) (38)*
Idiopathic hirsutism	9.9 (5-17) (14)*	4.9 (1.1-7.8) (14)	2.63 (1.6-5.2) (18)*	
Normal (early-mid-follicular phase)	6.1 (2.5-14) (16)	4.1 (1.3-6.9) (16)	1.7 (0.9-3.0) (21)	5.4 (3.0-8.5) (21)

Means were compared by Student's *t* test (in the case of luteinising hormone after logarithmic transformation of the data).

\**p* < 0.001.

Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 288 ng/l. Androstenedione: 1 nmol/l ≈ 286.4 ng/l.

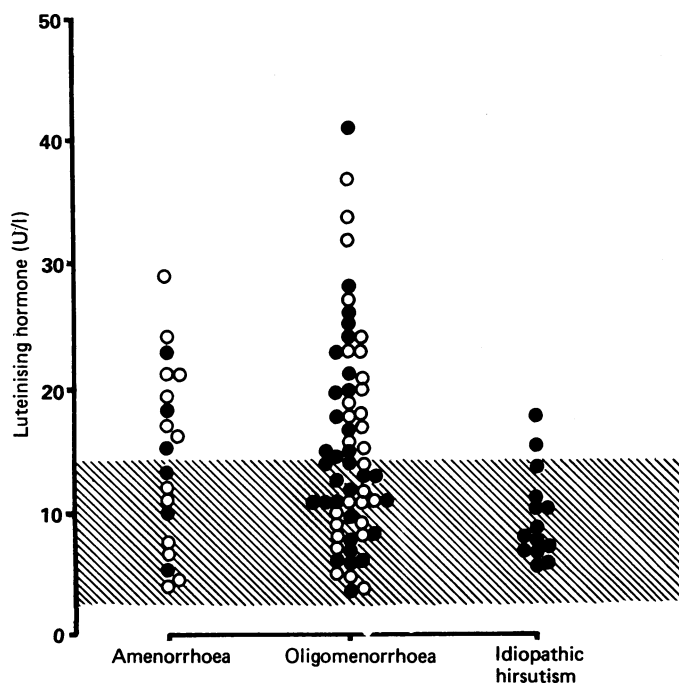


FIG 3—Serum luteinising hormone concentrations in three groups of women with polycystic ovaries. Closed circles represent patients with hirsutism or acne or both, and the open circles those with no clinical evidence of androgen excess. Normal range in the mid-follicular phase is shown by shaded area.

laparoscopy, but in a separate study the anatomical diagnosis on ultrasonography was validated by comparison with findings at laparoscopy with neither ultrasonographer (JA) nor gynaecologist (P Reginald) being aware of the other's observations. The results showed an excellent concordance (85% agreement) with ultrasound and laparoscopic findings (J Adams, P Reginald, R W Beard, S Franks, unpublished observations). Few patients have had histological examination of the ovaries, but in the seven cases in this series where this was undertaken the histological picture confirmed the ultrasound diagnosis.

In conclusion, the use of pelvic ultrasound has provided us with a precise and non-invasive method of assessing the presentation and prevalence of polycystic ovaries in women with amenorrhoea, oligomenorrhoea, or "idiopathic" hirsutism. We have shown that polycystic ovaries occur in 84 out of 148 (57%) patients with chronic anovulation and that 92% of women with hirsutism and regular cycles have polycystic ovaries. Our findings do not prove that polycystic ovaries are the cause of anovulation or hirsutism, but this seems very likely. The cause of polycystic ovaries remains unknown, but it has been suggested that the condition represents a non-specific response of the ovary to a variety of causes of chronic anovulation.<sup>3,5</sup> This, however, does not explain the findings of polycystic ovaries in women with idiopathic hirsutism, and there is, moreover, evidence for a primary disorder of the ovaries.<sup>4,12,13</sup> This may result in a secondary endocrine disturbance leading to anovulation, hirsutism, or both.

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## Risk factors for uterine fibroids: reduced risk associated with oral contraceptives

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### Abstract

Risk factors for pathologically confirmed uterine leiomyomas (fibroids) were investigated using data from the Oxford Family Planning Association study, a long term follow up study of women using various methods of contraception. For each of 535 women who had had a fibroid an individual control was selected who matched the patient on age, date of entry into the cohort, and family planning clinic at recruitment and who was alive (and still being followed up) at the date the patient underwent surgery for fibroids. Case-control analysis showed that reproductive experiences were closely linked to development of fibroids. Risk of fibroids decreased consistently with increasing number of term pregnancies; women with five term pregnancies had only a quarter of the risk of women who had had none. Risk also decreased consistently with increasing duration of oral contraceptive use; the risk of fibroids was reduced by some 31% in women who had used oral contraceptives for 10 years.

Risk was strongly related to weight: women who weighed under 55 kg had a particularly low risk, and overall the risk rose roughly 21% for each 10 kg increase. Cigarette smoking was associated with a decreased risk of fibroids; smokers of 20 cigarettes a day had a risk roughly two thirds that of non-smokers.

These risk factors have all previously been identified as risk factors for endometrial cancer; this strongly suggests that the underlying risk factor is "unopposed" oestrogen.

### Introduction

Uterine leiomyomas are the most common pelvic neoplasms and may be the most common of all tumours in women<sup>1,2</sup>; they are benign tumours of smooth muscle, commonly referred to as fibroids. Despite the importance of these tumours, little is known about their epidemiology or aetiology.

Fibroids are most commonly diagnosed during reproductive life, usually in the fourth to fifth decade,<sup>3</sup> and they tend to shrink or fibrose after the menopause.<sup>2</sup> Fibroids have been consistently associated with infertility: in one review of several large series totalling 1698 patients, 464 (27%) had a history of infertility.<sup>4</sup> Case reports have suggested that oral contraceptives may play a part in the development or growth of the tumours,<sup>5</sup> but a study of the records relating to a small series of women who had undergone hysterectomy, with and without fibroids, suggested that an inverse relation may in fact exist.<sup>6</sup> Although it is generally thought that fibroids rapidly increase in size during pregnancy,<sup>2</sup> detailed studies have failed to confirm this.<sup>7</sup>

Although not well documented, it is widely accepted that fibroids are much more common in American black women than American white women<sup>2</sup>: one suggested explanation for this is that black women have a higher prevalence of pelvic infections than white women and that such infections cause myometrial irritation leading to abnormal uterine growth.<sup>8</sup> This hypothesis is untested, and we could find no useful data on this issue.

Using data from the Oxford Family Planning Association cohort study, we have tested some of these hypotheses and provide other relevant information.

### Methods

The Oxford Family Planning Association study is a long term follow up study of white women who use different methods of contraception.<sup>9</sup> Between 1968 and 1974 17 032 women were recruited at 17 Family Planning Association clinics in England and Scotland. At the time of recruitment all women were married and aged 25-39 and were either using oral contraceptives and had done so for at least five months or were using the diaphragm or an intrauterine device (and had done so for at least five months) without previous use of oral contraceptives. At an admission interview the women were asked about their history of pregnancy, but no distinction was made between spontaneous and induced abortions; histories of oral contraceptive use were recorded in full, but histories of use of other contraceptive methods were restricted to the method they were using at the time of recruitment.

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