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Polycystic ovaries in pre and post-menopausal women

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Summary

OBJECTIVE Polycystic ovaries have been diagnosed in more than 20% of premenopausal women using ultrasound. The aim of this study was to determine whether polycystic ovaries exist in post-menopausal women.

DESIGN Two groups of women were studied; group 1 consisted of 18 post-menopausal volunteers and group 2 comprised 142 women, 94 of whom were post-menopausal who had recently undergone coronary angiography.

MEASUREMENTS Transabdominal and transvaginal ultrasound scans were performed and measurements made of uterine area, endometrial thickness and ovarian volume. The morphological appearance of the ovaries was also noted. Fasting blood samples were taken. Medical and menstrual questionnaires were completed.

RESULTS Polycystic ovaries were found in 8/18 (44%) of group 1 and 60/142 (42%) in group 2. Polycystic ovaries were detected in 35/94 (37%) of the post-menopausal women in group 2. Post-menopausal women with polycystic ovaries had larger ovaries containing more follicles compared with post-menopausal women with normal ovaries. Post-menopausal women with polycystic ovaries had higher serum concentrations of testosterone and triglycerides than had post-menopausal women with normal ovaries.

CONCLUSIONS Polycystic ovaries can be detected in post-menopausal women and have some of the same endocrine abnormalities which are evident in premenopausal women with polycystic ovaries, that is, raised serum concentrations of testosterone and triglycerides.

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Polycystic ovaries (PCO), as diagnosed by ultrasound, have been described in 22% of women in their reproductive years (Polson *et al*., 1988; Clayton *et al*., 1992; Farquhar *et al*., 1994). Polycystic ovaries are commonly associated with menstrual irregularity, acne, hirsutism and infertility (Gilling-Smith & Franks, 1993) and when polycystic ovaries as well as any of the above complaints are present, polycystic ovarian syndrome (PCOS) is said to exist. Recently, there have been reports of metabolic abnormalities in women with polycystic ovaries (Conway *et al*., 1992). These include raised serum concentrations of triglycerides and low density lipoprotein, lowered serum concentrations of high density lipoprotein (Wild *et al*., 1992) and evidence of insulin resistance (Barbieri, 1991), which are all recognized cardiac risk factors. A recent study has confirmed the association between ultrasonically diagnosed polycystic ovaries and angiographic coronary disease (Birdsall *et al*., 1996).

The cause of polycystic ovaries is unknown. Although exposure to high androgens from a variety of sources will cause the typical ultrasound appearances of polycystic ovaries, in most instances it is the ovary itself which is the source of these increased androgens (Wajchenberg *et al*., 1986). Defects at the hypothalamus, pituitary and ovary have all been described in women with polycystic ovaries. Because of the heterogeneous nature of the disorder (Balen *et al*., 1995), it may be that there is more than one cause. A genetic basis for the condition has also been proposed with an autosomal dominant mode of inheritance (Carey *et al*., 1993) being one possibility.

The natural history of polycystic ovaries is unknown since ultrasound as a means of diagnosis had been described only since 1981 (Swanson *et al*., 1981). Polycystic ovaries have been described in young girls and adolescents (Bridges *et al*., 1993) and at times of ovarian quiescence during the reproductive years, such as during lactation (Farquhar *et al*., 1994), oral contraceptive use (Farquhar *et al*., 1994), gonadotrophin-releasing hormone analogue use (MacDougall *et al*., 1993) and hypothalamic-hypogonadism (Shoham *et al*., 1992). These observations would suggest that the condition is independent of gonadotrophins and folliculogenesis. Polycystic ovaries in post-menopausal women have not been previously described. There are two reasons for an interest in such an observation; first, it might provide a further clue as to the aetiology of polycystic ovaries and, secondly, a group of women at risk of heart disease may be identified.

Methods

Two groups of women were studied. Group 1 was made up of 18 volunteers from hospital staff who formed a small pilot study prior to studying a larger group of women. The entry criteria were: age greater than 50 as well as absence of menses for one year or more, no major gynaecological surgery and no prior diagnosis of PCO.

Group 2 consisted of women aged 60 years or less, who had undergone coronary angiography for investigation of chest pain (86%) or valvular heart disease (4%) in Auckland in the preceding 2 years. The only exclusion criterion was previous bilateral oophorectomy. This group was part of another study examining the relation between heart disease and PCO (Birdsall *et al*., 1996).

Ethical approval was granted by the Auckland Area Health Board Ethics Committee. Menopause was defined as amenorrhoea for one year or, if a hysterectomy had been performed or the woman was on hormone replacement therapy, a FSH level >20 U/l. Written informed consent was obtained. Women who were still menstruating were given an appointment in the follicular phase of their menstrual cycle (days 5–9). Data were collected on reproductive and medical histories.

Blood pressure was recorded whilst seated and the body mass index (weight in kilograms divided by the square of the height in metres) was calculated. The circumference of the waist at the level of the umbilicus and the maximal circumference at the level of the hips was measured to the nearest centimetre, and the values were rounded down and expressed as the waist/hip ratio. An assessment of hirsutism was made using the Ferriman–Gallwey score (Ferriman & Gallwey, 1961).

The transabdominal ultrasound examinations were performed using a full bladder technique and a 3·5 MHz real time scanner (Toshiba 270 or Toshiba Capasee). The uterus was measured in 2 planes. The ovaries were measured in 3 planes and ovarian volumes were calculated using a simplified formula for a prolate ellipse ($\frac{1}{2} \times$ length $\times$ width $\times$ thickness). The presence, size and number of ovarian follicles were noted. Polycystic ovaries were defined by modified Adam's criteria (Adams *et al*., 1986) namely 8 or more cysts of 2–8 mm diameter associated with an increase in ovarian stroma (Fig. 1). In consenting patients (71·3%), a transvaginal ultrasound was performed using a 5 MHz probe. Ovaries containing follicles of greater than 10 mm were excluded from analyses of both ovarian volume and follicular diameter. Two observers (MB and CF) performed the ultrasound examinations. The inter-observer error was assessed over the first 18 patients and was within 10% for measurements with consistent agreement on morphology.

Overnight fasting blood samples were drawn for measurement of FSH, LH, sex hormone binding globulin (SHBG), testosterone, insulin, C-peptide, glucose, lipids, lipoprotein(a), fibrinogen and ferritin. Testosterone was measured using a commercial direct radioimmunoassay kit (Diagnostic Products Corperation, USA).

Where values exceeded the normal female range they were reassayed using an ether extraction method. The interassay precision was 7·1% ($n = 30$). LH and FSH were measured using the Amerlite immunometric enhanced luminescence method (Kodak, UK). The interassay precision for LH was 8·3% ($n = 30$). The interassay precision for FSH was 7·9% ($n = 30$). The normal range for FSH for premenopausal women is 1·0–8·0 IU/l and for post-menopausal women 18·0–120 IU/l. SHBG was measured using a saturation and displacement analysis method. The interassay precision was 6·8% ($n = 30$). Plasma from fasting subjects was analysed for cholesterol, triglycerides, HDL cholesterol and apolipoproteins A1 and B in the Greenlane Hospital laboratory which participates in the standardization programmes of the Centers for Disease Control in Atlanta. Insulin and C-peptide were measured using a radioimmunoassay (Novo Nordisk, Copenhagen). The inter-assay precision was 5·4% for insulin and 6·7% for C-peptide.

For continuous variables the data were analysed using Student's *t*-test. Discrete variables were analysed using χ^2-tests.

Results

Group 1 consisted of 18 women with a mean age 56·9 years and a range of 51–65 years. Polycystic ovaries were found in 44% (8/18) of the women in group 1. The women with PCO were found to be more hirsute ($P = 0{\cdot}04$) and have larger ovaries (5·0 *vs* 3·17 cm^2, $P = 0{\cdot}03$) which contained more follicles (8·6 *vs* 2·1, $P = 0{\cdot}0001$) than women with normal ovaries. Significantly higher serum concentrations of testosterone were also observed (1·3 *vs* 0·83 nmol/l, $P = 0{\cdot}04$).

One hundred and forty-three women comprised group 2 of the study. The mean age in the whole group was 53·2 years with a range from 36 to 60 years. One woman's ovaries could not be visualized by either transabdominal or transvaginal ultrasound and her results are excluded from the analysis. Polycystic ovaries were diagnosed using ultrasound in 42·3% (60/142). There were 66·2% (94/142) post-menopausal women and 33·8% (48/142) premenopausal women. Polycystic ovaries were detected in 37·2% (35/94) of post-menopausal women and in 52% (25/48) of premenopausal women. In women whose ovaries could not be visualized adequately using transabdominal ultrasound (32/142, 22·5%), the transvaginal appearances of the ovaries were used to determine morphology. There was no difference in the ultrasound findings when the transabdominal and transvaginal techniques were compared. No significant pelvic pathology was diagnosed using ultrasound

in this study. The ultrasound findings are shown in Tables 3 and 4.

Laboratory data are shown in Tables 1 and 2. Premenopausal women with PCO had higher C-peptide levels as well as ferritin and fibrinogen levels. Post-menopausal women with PCO had higher serum concentrations of testosterone and triglycerides.

The women in group 2 with polycystic ovaries were more hirsute with Ferriman-Gallwey scores of 5·0 (3·8 SD) *vs* 3·8 (3·0 SD) ($P = 0{\cdot}03$); had undergone a hysterectomy more frequently ($P = 0{\cdot}02$) and required lipid modifying medications more frequently ($P = 0{\cdot}01$) when compared to the women with normal ovaries in group 2. We did not observe a significant

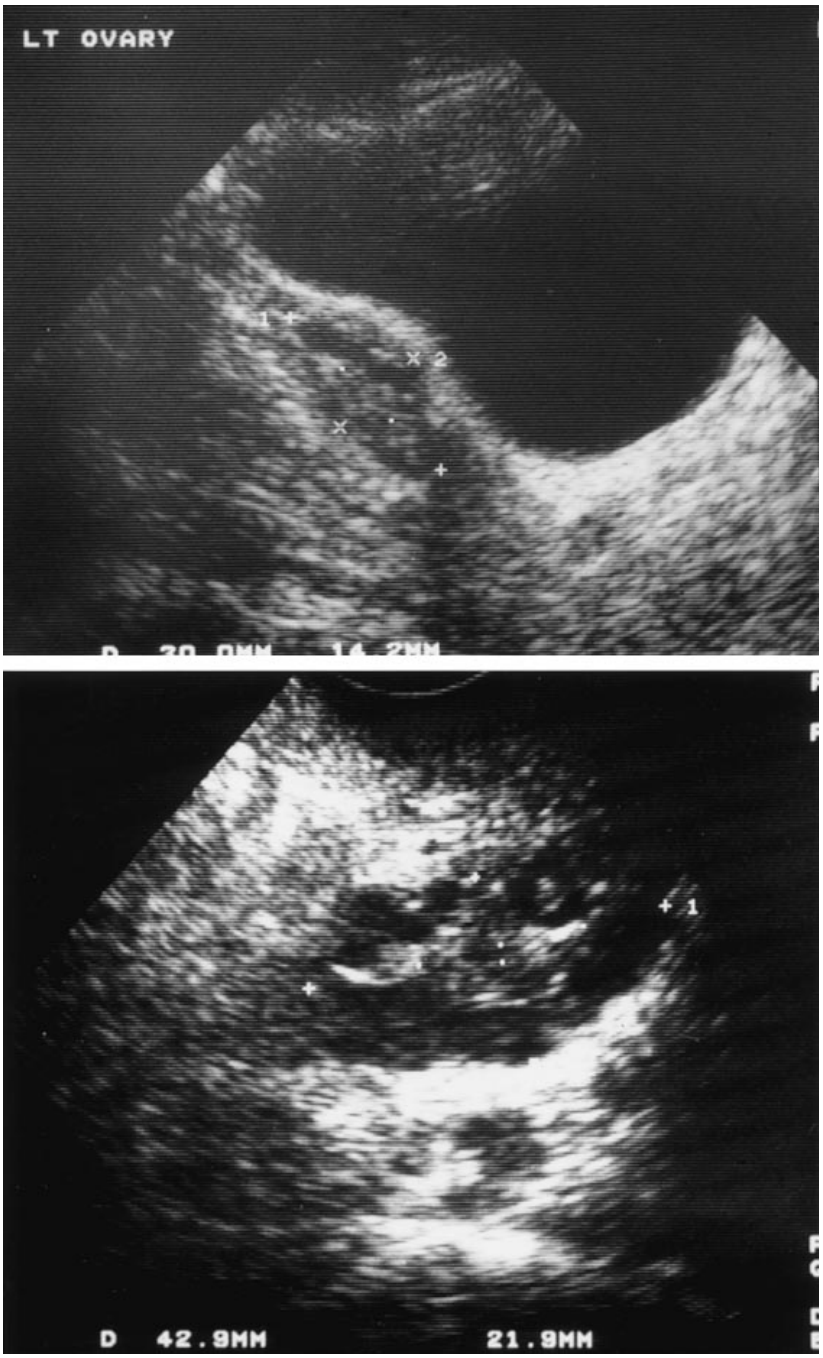

Fig. 1. The ultrasound appearance of post-menopausal polycystic ovaries.

Table 1 Laboratory findings in premenopausal women with polycystic ovaries and normal ovaries (group 2) (means (SD))

	Polycystic ovaries ($n = 25$)	Normal ovaries ($n = 23$)	*P*-value
FSH (IU/l)	9·47 (5·46)	8·29 (4·53)	NS
LH (IU/l)	6·82 (4·83)	6·45 (6·24)	NS
Testosterone (nmol/l)	1·30 (0·81)	0·98 (0·62)	NS
Free testosterone (pmol/l)	29·4 (18·4)	21·8 (13·8)	NS
SHBG (nmol/l)*	66·5 (23·1)	66·0 (25·6)	NS
Fasting glucose (mmol/l)	5·41 (0·78)	5·14 (1·94)	NS
Fasting insulin (MIU/l)	11·19 (8·58)	9·35 (4·44)	NS
Fasting C-peptide (nmol/l)	0·51 (0·22)	0·41 (0·15)	0·05
Cholesterol (mmol/l)	5·63 (1·24)	4·98 (1·45)	NS
Triglyceride (mmol/l)	1·75 (0·88)	1·29 (0·76)	NS
HDL (mmol/l)†	1·21 (0·57)	1·11 (0·54)	NS
LDL (mmol/l)‡	3·21 (1·44)	2·87 (1·47)	NS
Apolipoprotein A1(g/l)	1·07 (0·37)	1·08 (0·34)	NS
Apolipoprotein B(g/l)	1·25 (0·36)	1·11 (0·30)	NS
Lipoprotein(a) (mg/l)	338 (396)	216 (242)	NS
Ferritin (μg/l)	72·2 (59·1)	42·6 (30·4)	0·04
Fibrinogen (g/l)	2·57 (0·87)	1·57 (1·24)	0·002

* Sex hormone binding globulin.
† High density lipoprotein cholesterol.
‡ Low density lipoprotein cholesterol.

difference in body mass indices, or history of infertility or menstrual disturbance. Hormone replacement therapy was being currently taken by 23/60 women with PCO and 19/82 women with normal ovaries ($P = 0·06$).

When the data were analysed according to menopausal status, post-menopausal women with PCO were found to require lipid modifying drugs more frequently than post-menopausal women with normal ovaries (13/35 *vs* 8/

Table 2 Laboratory findings in post-menopausal women with polycystic ovaries and normal ovaries (group 2) (means (SD))

	Polycystic ovaries ($n = 35$)	Normal ovaries ($n = 59$)	*P*-value
FSH (IU/l)	47·48 (15·57)	47·30 (20·19)	NS
LH (IU/l)	22·14 (7·29)	22·24 (10·83)	NS
Testosterone (nmol/l)	1·25 (0·59)	0·96 (0·54)	0·02
Free testosterone (pmol/l)	28·3 (14·3)	21·8 (13·7)	0·03
SHBG (nmol/l)*	67·7 (22·4)	67·8 (20·6)	NS
Fasting glucose (mmol/l)	5·06 (2·20)	5·37 (2·05)	NS
Fasting insulin (MIU/l)	9·97 (4·35)	9·68 (5·40)	NS
Fasting C-peptide (nmol/l)	0·51 (0·14)	0·46 (0·17)	NS
Cholesterol (mmol/l)	5·90 (1·76)	5·86 (1·48)	NS
Triglyceride (mmol/l)	1·99 (1·28)	1·48 (0·81)	0·02
HDL (mmol/l)†	1·11 (0·55)	1·30 (0·56)	NS
LDL (mmol/l)‡	3·20 (1·92)	3·48 (1·50)	NS
Apolipoprotein A1(g/l)	1·15 (0·36)	1·23 (0·32)	NS
Lipoprotein(a) (mg/l)	326 (333)	327 (302)	NS
Ferritin (μg/l)	67·9 (56·2)	78·4 (65·8)	NS
Fibrinogen (g/l)	2·67 (0·83)	2·29 (1·29)	NS

* Sex hormone binding globulin.
† High density lipoprotein cholesterol.
‡ Low density lipoprotein cholesterol.

Table 3 Transabdominal ultrasound findings in premenopausal and post-menopausal women (group 2) (means (SD))

	Premenopausal women ($n = 48$)	Post-menopausal women ($n = 94$)	*P*-value
Uterine size (cm^2)	41·4 (13·9)	27·6 (11·4)	0·0001
Endometrial thickness (mm)	6·3 (2·9)	4·7 (2·5)	0·02
No ovaries visualized	7/48 (14·6%)	25/94 (26·6%)	NS
Any ovaries visualized	40/48 (83·3%)	69/94 (73·4%)	NS
Average ovarian volume (cm^3)	8·1 (3·8)	5·0 (2·9)	0·0001
Average number of follicles	5·8 (3·5)	3·7 (3·5)	0·001
Size of largest follicle (mm)	7·7 (5·4)	4·2 (1·8)	0·0001

59, $P = 0{\cdot}02$) and were more hirsute with Ferriman–Gallwey scores of 5·3 (3·9) *vs* 3·4 (2·5) ($P = 0{\cdot}005$) but otherwise no significant clinical differences were observed. There was no difference in the number of post-menopausal women with PCO currently taking HRT compared to post-menopausal women with normal ovaries (11/35 *vs* 13/48, $P =$ NS).

One post-menopausal participant in this study (FSH = 28 IU/l) had a hysterectomy and bilateral salpingo-oophorectomy shortly after the study was completed. She was diagnosed as having polycystic ovaries on ultrasound and histological examination of her ovaries revealed marked stromal hyperplasia, thickening of the capsule, multiple inclusion cysts and areas of luteinized stromal cells (Fig. 2). The endometrium was hyperplastic despite the patient having received high dose progestogens. The mean ovarian volume (12 cm^3) was also larger than would be expected for a post-menopausal woman.

Discussion

This study describes for the first time polycystic ovaries, as diagnosed by ultrasound, in post-menopausal women. We found that women with polycystic ovaries after the climacteric were more hirsute, having higher serum concentrations of testosterone and triglycerides and have larger ovaries compared with post-menopausal women with normal ovaries. These are the same findings as have been reported in premenopausal women (Balen *et al*., 1995). We were unable to show these same differences in the premenopausal women studied; however, the small numbers involved probably accounts for this finding. Infertility and menstrual disturbance did not occur more commonly in the women with PCO; however, this may be because these women have polycystic ovaries alone and not the polycystic ovary syndrome or because of difficulties with recall of menstrual history from many years previously. Hysterectomy was performed more frequently in women with PCO suggesting that menstrual disturbance, which is the most frequent reason for hysterectomy, may occur more commonly in women with PCO. The high prevalence of polycystic ovaries found is almost certainly due to the populations studied, most of whom were undergoing coronary angiography because of a

Table 4 Ultrasound findings according to menopausal status and ovarian appearances (Group 2)

	Premenopausal women ($n = 48$) Means (SD)			Post-menopausal women ($n = 94$) Means (SD)		
	PCO ($n = 25$)	Normal ovaries ($n = 23$)	*P*-value	PCO ($n = 35$)	Normal ovaries ($n = 59$)	*P*-value
Ovarian volume (cm^3)	9·19 (3·49)*	5·34 (2·39)	0·0001	6·38 (3·26)*	3·7 (2·14)	0·0001
Number of follicles	9·66 (0·99)†	2·68 (1·51)	0·0001	9·01 (1·09)†	1·7 (1·4)	0·0001
Uterine size (cm^3)	42·1 (13·7)‡	40·7 (14·9)	NS	29 (13·9)‡	26·9 (10·2)	NS
Endometrial thickness (mm)	6·6 (2·6)§	5·9 (3·3)	NS	4·2 (2·5)§	5·0 (2·6)	NS

* Polycystic ovaries in premenopausal women were significantly larger than polycystic ovaries in post-menopausal women ($P = 0{\cdot}002$).
† More follicles were seen in premenopausal women with PCO than in post-menopausal women with PCO ($P = 0{\cdot}02$).
‡ Premenopausal women with PCO had significantly larger uteri than post-menopausal women with PCO ($P = 0{\cdot}0001$).
§ Premenopausal women with PCO had thicker endometrium compared with post-menopausal women with PCO ($P = 0{\cdot}0001$).

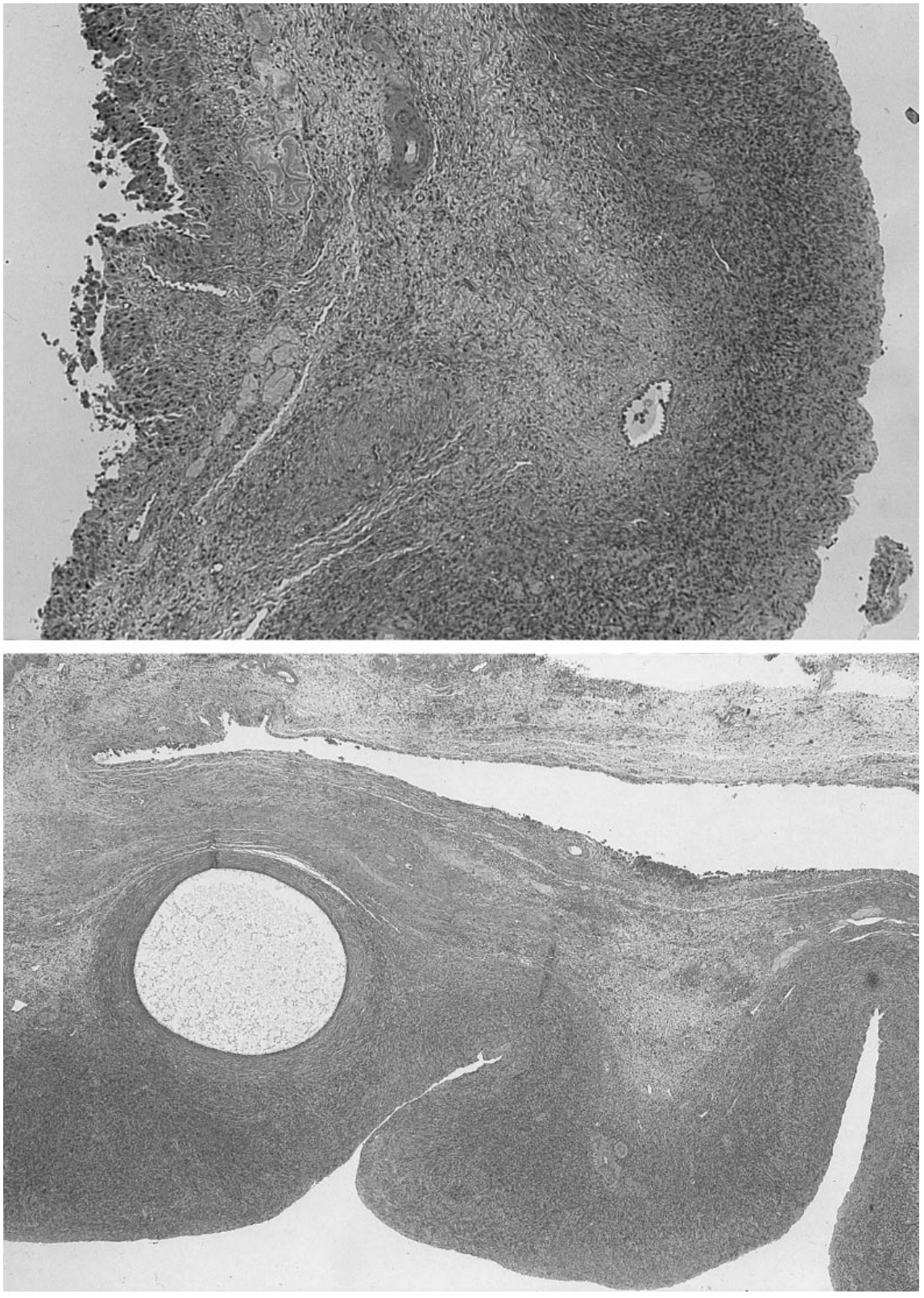

Fig. 2 The histological appearance of post-menopausal polycystic ovaries showing luteinized stromal cells and stromal hyperplasia.

clinical suspicion of heart disease. Polycystic ovaries may be associated with coronary artery disease because of the insulin resistance and lipid abnormalities observed in women with PCO.

It is not clear what the cystic areas seen on ultrasound may be as the post-menopausal ovary is thought to be devoid of follicles (Richardson *et al*., 1987). The 'cysts' may be follicles which are slowly resolving or be variations in the echotexture of the ovaries consistent with stromal and hilar cell hyperplasia. Histological studies on premenopausal polycystic ovaries have shown a doubling in the number of ripening and atretic follicles (Hughesdon, 1982). The 'cysts' observed in this study may be some remaining atretic follicles. An ultrasound study examining post-menopausal women prior to oophorectomy correlating the ultrasound and the histology findings may clarify this question.

An explanation for these findings may be that the women studied were 'peri-menopausal' and the ovarian ultrasound appearances would return to normal with time. A follow-up study in 5 years time would resolve this issue. It is possible that these ovaries may represent ovaries in the early years of the menopause before the depletion of the follicles is complete.

Post-menopausal women were found to have smaller uteri and ovaries and have thinner endometriums when compared with premenopausal women (Table 3). We have included these data as we believe they validates the findings in this study.

What is the importance of the finding of post-menopausal women with polycystic ovaries? First, this observation provides an interesting insight into the natural history of PCO as it is unlikely to arise *de novo* after the menopause so it is therefore likely that 'once a polycystic ovary always a polycystic ovary'. Post-menopausal PCO implies that folliculogenesis is not a prerequisite for the condition and that the problem within the ovary may be associated with the ovarian stroma, such as an enzymal abnormality as proposed by Barnes *et al*. (1989). The ultrasound appearance of polycystic ovaries is associated with an increased risk of metabolic abnormalities and coronary disease and it would be useful to be able to identify those post-menopausal women who are at more risk. Post-menopausal polycytic ovaries would thus appear to be an important finding.

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