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Polycystic ovary syndrome and cancer

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The polycystic ovary syndrome (PCOS) is the most common endocrine disturbance affecting women, but disagreements in diagnostic criteria make it difficult to compare epidemiological studies on long-term health risks such as cancer. The association between PCOS and endometrial adenocarcinoma has been reported for many years. Although the degree of risk has not been clearly defined, it is generally accepted that for women with PCOS who experience symptoms of amenorrhoea or oligomenorrhoea, the induction of artificial withdrawal bleeds to prevent endometrial hyperplasia is prudent management. Studies examining the relationship between PCOS and breast carcinoma have not always identified a significantly increased risk, although one recent study examined the standardized mortality rate (SMR) calculated for patients with PCOS compared with the normal population and found that the SMR for all neoplasms was 0.91 (95% CI 0.60–1.32) and for breast cancer 1.48 (95% CI 0.79–2.54). Few studies have addressed the possibility of an association between polycystic ovaries and ovarian cancer, and the results are conflicting and generally reassuring.

Key words: breast cancer/endometrial cancer/ovarian cancer/polycystic ovaries

TABLE OF CONTENTS

Introduction

The polycystic ovary syndrome (PCOS) is the commonest endocrine disturbance affecting women, yet there is still lack of consensus on its definition. It has long been recognized that the presence of enlarged ovaries with multiple small cysts (2–8 mm) and a hypervascularized, androgen-secreting stroma are associated with signs of androgen excess (hirsutism, alopoecia, acne), obesity and menstrual cycle disturbance (oligomenorrhoea or amenorrhoea). The European view generally is that the syndrome encompasses any of the above-mentioned signs, symptoms or endocrine abnormalities (elevated serum androgen and/or LH concentrations) (Balen *et al.*, 1995; Homburg, 1996). In North America, the consensus is that the syndrome is denoted by the combination of hyperandrogenism and ovulatory dysfunction, in the absence of non-classical adrenal hyperplasia, without necessarily having to identify the presence of polycystic ovaries by ultrasound scan (Dunaif, 1997). The European definition, which we have designated as PCO1, is broader than that of the USA (designated PCO2) (Balen, 1999). There is considerable heterogeneity of symptoms and signs among women with PCOS, and for an individual these may change over time. The PCOS is familial, and various aspects of the syndrome may be differentially inherited (Franks *et al.*, 1997). Furthermore, polycystic ovaries can exist without clinical signs of the syndrome, which may then become expressed over time.

Ovarian dysfunction leads to the main signs and symptoms of PCOS, and the ovary is influenced by external factors—in particular the gonadotrophins, insulin and other growth factors—which are dependent upon both genetic and environmental influences. Approximately 20% of women of reproductive age will have polycystic ovaries on ultrasound scan (Polson *et al.*, 1988), while up to 10% will have symptoms consistent with the diagnosis of PCOS (Futterweit and Mechanick, 1988). There are long-term risks of developing diabetes and cardiovascular disease for PCOS patients (recently reviewed by Rajkowha *et al.*, 2000). The long-term risk of endometrial hyperplasia and endometrial carcinoma due to chronic anovulation and unopposed oestrogen has long been recognized; similarly, there may be an increased risk of breast carcinoma. The multifactorial nature of the syndrome, combined with its heterogeneous presentation, makes it difficult to ascertain which factors (i.e. hyperinsulinaemia, elevated serum concentrations of growth factors, obesity or genetic predisposition) cause the most significant risk with respect to the development of cancer.

Endometrial cancer

While endometrial adenocarcinoma is the second most common female genital malignancy, only 4% of cases occur in women <40 years of age. The risk of developing endometrial cancer has been shown to be adversely influenced by a number of factors including obesity, long-term use of unopposed oestrogens, nulliparity and infertility (Henderson *et al.*, 1983; Dahlgren *et al.*, 1989, 1991). In fact, the relative risk of endometrial cancer is 1.6 in women with a menarche before the age of 12 years, and 2.4 in women with their menopause after the age of 52 years (Elwood *et al.*, 1977). Women with endometrial carcinoma have fewer births compared with controls (Elwood *et al.*, 1977), and it has also been demonstrated that infertility *per se* gives a relative risk of 2 (MacMahon, 1974). Hypertension and type II diabetes mellitus have long been linked to endometrial cancer, with relative risks of 2.1 and 2.8 respectively (Elwood *et al.*, 1977); these conditions are now known also to be associated with PCOS.

The association between PCOS and endometrial adenocarcinoma has been reported for many years. One report of 16 cases (Jackson *et al*., 1957) indicated such factors as age ranging from 27 to 48 years, a high rate of prolonged amenorrhoea, obesity and hypertension and nulliparity in 13 of the 15 married women. In another study (Coulam *et al*., 1983), the risk of developing endometrial carcinoma was examined in a group of 1270 patients who were diagnosed as having 'chronic anovulation syndrome'. The defining characteristics of this group included pathological or macroscopic evidence of the Stein–Leventhal syndrome, or a clinical diagnosis of chronic anovulation. This study identified the excess risk of endometrial cancer to be 3.1 [95% confidence interval (CI) 1.1–7.3], and proposed that this might be due to abnormal concentrations of unopposed oestrogen. Other authors have expanded this theory by suggesting that hyperandrogenism and hyperinsulinaemia may further increase the potential for neoplastic change in the endometrium through their effects on concentrations of sex hormone-binding globulin (SHBG), insulin-like growth factor-1 (IGF-1) and circulating oestrogens (Gibson, 1995; Meirow and Schenker, 1996).

The true risk of endometrial carcinoma in women with PCOS however is difficult to ascertain. Studies to date have been limited by the relatively small numbers of cases of endometrial carcinoma identified specifically in women with PCOS, and thus the confidence limits for relative risks are very wide (Coulam *et al.*, 1983; Shu *et al.*, 1993). Consideration must also be given to the fact that in many epidemiological studies, women with PCOS have been classed under a general heading of 'hormonal' or 'ovarian' infertility, and thus risks calculated for this group will include other conditions, and additionally will only represent the risk for the subset of women with PCOS who are infertile (Ron El *et al.*, 1987; Brinton *et al.*, 1989; Dahlgren *et al.*, 1991; Escobedo *et al.*, 1991).

Endometrial hyperplasia may be a precursor to adenocarcinoma, with cystic glandular hyperplasia progressing in perhaps 0.4% of cases and adenomatous hyperplasia in up to 18% of cases over a time period of 2 to 10 years, although a precise estimate of rate of progression is impossible to determine (Chamlian and Taylor, 1970). In a study of 97 women under the age of 36 years with adenomatous or atypical adenomatous hyperplasia, 25% were found to have typical polycystic ovaries confirmed by biopsy. The mean age of the 24 women in this group was 25.7 years and all were nulliparous (23 were married). In 12 patients the diagnosis of polycystic ovaries was made at the time of hysterectomy (at which time two were found to have carcinoma). Treatment was by wedge resection of the ovaries in the other 12 patients, of whom eight had follow-up endometrial curettage and only three had persistent hyperplasia (one of which progressed to adenocarcinoma). One patient was found on initial curettage to have focal adenocarcinoma, which regressed after wedge biopsy, following which a normal pregnancy resulted from clomiphene citrate treatment. The other patients all had problems with infertility; some were treated with clomiphene citrate, although results were poor (Chamlian and Taylor, 1970).

Other authors have also reported conservative management of endometrial adenocarcinoma in women with PCOS. The rationale is that cancer of the endometrium often presents at an early stage, is well differentiated, of low risk of metastasis and therefore is not perceived as being life-threatening (McDonald *et al.*, 1977; Farhi *et al.*, 1986; Kung *et al.*, 1997). Furthermore, these women are young and usually desirous of fertility. One group (Fechner and Kaufman, 1974) reported four cases of well-differentiated carcinoma in women aged 21–34 years. Two of these women had a hysterectomy, and one had a wedge resection, a subsequent regular menstrual cycle and no recurrence after 12 years, but she remained nulliparous. The fourth woman, aged 21 years, was treated with both wedge resection and clomiphene citrate but eventually required hysterectomy for metromenorrhagia 2 years later, at which time there was still a superficial adenocarcinoma. The authors suggested that if the histology indicated a well-differentiated lesion then a conservative approach was acceptable, whilst poorly differentiated adenocarcinoma in a young woman had a worse prognosis and warranted hysterectomy (Fechner and Kaufman, 1974). Others (Farhi *et al.*, 1986) agreed with this suggestion and used a combination of curettage and high-dose progestogens in three patients, one of whom later bore two children; nevertheless, seven of the ten patients that they reported required hysterectomy.

Others have also advocated a conservative approach. Indeed, one group (Muechler *et al.*, 1986) went as far as to induce ovulation with human menopausal gonadotrophins in a woman who had a well-differentiated adenocarcinoma treated with medroxyprogesterone acetate for 6 months, following which there was persistent adenomatous hyperplasia but no malignancy. The patient conceived twice and had a miscarriage of twins, followed by a successful singleton pregnancy after which a hysterectomy was performed (histology again showed adenomatous hyperplasia but no malignancy). Another case employed hysteroscopically guided biopsy and endometrial curettage with clips applied to the Fallopian tubes in order to prevent retrograde spread of tumorous cells (Kung *et al.*, 1997). In this case laparoscopic ovarian diathermy was used to reduce ovarian activity, with subsequent follow-up treatment first with progestins and then with the combined oral contraceptive pill (Kung *et al.*, 1997).

In general, however, the literature on women with PCOS and endometrial hyperplasia or adenocarcinoma suggests that this group of patients have a poor prognosis for fertility. This may be because of the factors that predisposed to the endometrial pathology—chronic anovulation combined often with severe

obesity—or secondary to the endometrial pathology disrupting potential embryonic implantation. Case studies and small series of cases treated successfully without recourse to hysterectomy may be subject to publication bias and may not represent widespread medical opinion. Thus, a more traditional and radical surgical approach is suggested as the safest way to prevent progression of the cancer (Jafari *et al.*, 1978).

Although the degree of risk has not been clearly defined, it is generally accepted that for women with PCOS who experience symptoms of amenorrhoea or oligomenorrhoea, the induction of artificial withdrawal bleeds to prevent endometrial hyperplasia is prudent management. Indeed, we consider it important that women with PCOS shed their endometrium at least every 3 months. For those with oligomenorrhoea/amenorrhoea who do not wish to use cyclical hormone therapy we recommend an ultrasound scan to measure endometrial thickness, and morphology every 6–12 months (depending upon menstrual history). An endometrial thickness >10 mm in an amenorrhoeic woman warrants an artificially induced bleed, which should be followed by a repeat ultrasound scan and endometrial biopsy if the endometrium has not been shed.

Breast cancer

Obesity, hyperandrogenism, and infertility occur frequently in PCOS, and are features known to be associated with the development of breast cancer. However, studies examining the relationship between PCOS and breast carcinoma have not always identified a significantly increased risk (Coulam *et al.*, 1983; Gammon and Thompson, 1991; Anderson *et al.*, 1997). In the first of these studies (Coulam *et al*., 1983), a relative risk of 1.5 (95% CI 0.75–2.55) was calculated for breast cancer in a group of women with chronic anovulation, but this was not statistically significant. After stratification by age however, the relative risk was found to be 3.6 (95% CI 1.2–8.3) in the postmenopausal age group. Conversely, others (Gammon and Thompson, 1991) reported a reduced risk of breast cancer in women with PCOS, finding an odds ratio of 0.52 (95% CI 0.32–0.87). This study however is difficult to interpret as the prevalence of PCOS as identified by a self-assessed questionnaire was found to be only 0.49% among 4697 cases, and only 0.94% in 4657 controls. These prevalence rates fall well below estimates expected for the normal population, and indicate that the method used to determine the presence of PCOS was not sufficiently sensitive. Similar comments could be applied to the final large prospective study designed to examine the development of breast carcinoma in postmenopausal women (Anderson *et al*., 1997). The prevalence of PCOS in their cohort of 34 835 women was found to be only 1.35%, and these authors determined that PCOS was not associated with an increased risk of breast carcinoma in this cohort. In this series, although women with PCOS were 1.8 times as likely to report benign breast disease than control women ($P < 0.01$), they were not more likely to develop breast carcinoma [relative risk (RR) = 1.2; 95% CI = 0.7–2]. Adjustment for age at menarche, age at menopause, parity, oral contraceptive use, body mass index, waist-to-hip ratio, and family history of breast carcinoma lowered the RR to 1 (95% CI = 0.6–1.9.) Thus, despite the high-risk profiles of some women with PCOS, these results do not suggest that the syndrome *per se* is associated with an increased risk of postmenopausal breast carcinoma (Anderson *et al.*, 1997).

More recently, a series of 786 women with PCOS was reported in the UK; the women were traced from hospital records after histological diagnosis of polycystic ovaries between 1930 and 1979 (Pierpoint *et al.*, 1998). Mortality was assessed from the national registry of deaths and standardized mortality rates (SMR) calculated for patients with PCOS compared with the normal population. The average follow-up period was 30 years. The SMR for all neoplasms was 0.91 (95% CI 0.60–1.32) and for breast cancer was 1.48 (95% CI 0.79–2.54). In fact, breast cancer was the leading cause of death in this cohort.

Ovarian cancer

In recent years there has been much debate about the risk of ovarian cancer in women with infertility, particularly in relation to the use of drugs to induce superovulation for assisted conception procedures. Inherently the risk of ovarian cancer appears to be increased in women who have multiple ovulations; that is, those who are nulliparous (possibly because of infertility) with an early menarche and late menopause. Thus, it may be that inducing multiple ovulations in women with infertility will increase their risk (see review by Nugent *et al.*, 1998), though this notion is by no means proven. Epithelial malignant transformation may also occur secondary to perturbations in the local concentrations of steroid hormones or growth factors, for example epidermal growth factor (EGF) (Berchuck *et al.*, 1990). The majority of malignant ovarian tumours appear to have steroid hormone receptors (62% for oestrogen, 49% progesterone and 69% for androgen; Rao and Slotman, 1991). Cytokines may also play a role in malignant transformation. The various interactions of altered local ovarian factors and environmental factors have been reviewed recently (Riman *et al.*, 1998). As many of these factors are altered in PCOS, one might suspect that these women would be at increased risk. On the other hand, women with PCOS who are oligo-/anovulatory might therefore be expected to be at low risk of developing ovarian cancer if it is lifetime number of ovulations rather than pregnancies that is critical.

Ovulation induction to correct anovulatory infertility aims to induce unifollicular ovulation, and so in theory should raise the risk of a woman with PCOS to that of a normally ovulating woman. The polycystic ovary is notoriously sensitive to stimulation however, and it is only in recent years with the development of high-resolution transvaginal ultrasonography that the rate of unifollicular ovulation has attained acceptable levels (Balen, 1998). The use of clomiphene citrate and gonadotrophin therapy for ovulation induction in the 1960s, 1970s and 1980s resulted in many more multiple ovulations (and indeed multiple pregnancies) than in more recent times, and might therefore present with an increased rate of ovarian cancer when these women reach the age of greatest risk.

Few studies have been reported which address the possibility of an association between polycystic ovaries and ovarian cancer. The results are conflicting, and generalizability is limited due to problems with the study designs. One group (Coulam *et al*., 1983) showed no increased risk of ovarian carcinoma among anovulatory women, whilst others (Schildkraut *et al*., 1996) suggested that PCOS conferred a relative risk of 2.5 (95% CI 1.1–5.9) for

epithelial ovarian cancer in their case–control study. The prevalence of PCOS as determined by questionnaire was found to be 1.5% in cases, and 0.6% in controls. The authors acknowledged that the small number of women with PCOS ($n = 31$) limited the interpretation of their findings, and that consideration must be given to the possibility of recall bias in subjects affected with ovarian cancer. In one large UK study (Pierpoint *et al.*, 1998) the SMR for ovarian cancer was 0.39 (95% CI 0.01–2.17).

Conclusions

Polycystic ovary syndrome is common, and the criteria used for its diagnosis are varied, although these are becoming more unified in the literature. Epidemiological studies often incorporate patients with infertility or ovarian dysfunction, which may result in imprecision of diagnostic categories. That there is an association between PCOS and endometrial cancer there is no doubt. Patients with oligomenorrhoea/amenorrhoea should therefore be screened by ultrasound and be given therapy to promote regular endometrial shedding. If a diagnosis of endometrial hyperplasia is made, then conservative treatment and follow-up is appropriate. Published data exist relating to a few cases which indicate that patients with well-differentiated adenocarcinoma of the endometrium may also be treated conservatively with progestogens and ovulation induction, although only a few pregnancies are reported and the safest approach is probably still hysterectomy. Patients should be counselled carefully before a decision is taken. Ovarian preservation may permit surrogacy at a later date.

An association between PCOS and ovarian cancer seems unlikely, leaving aside the putative association with ovulation-inducing drugs, which is an issue that should not apply to the modern approach to unifollicular ovulation induction in patients with PCOS and anovulatory infertility. A link between PCOS and cancer of the breast appears probable on both theoretical grounds and epidemiological evidence, although not all studies agree.

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