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META-ANALYSIS ***Gynaecology***

Evaluating the association between endometrial cancer and polycystic ovary syndrome

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BACKGROUND: Given the current lack of clarity in the published literature, we performed a systematic review of the literature to determine the exact strength of the association between polycystic ovary syndrome (PCOS) and endometrial cancer (EC).

METHODS: All published studies on the association between PCOS and EC identified through MEDLINE (1966–April 2011), EMBASE (1980–April 2011) and Cochrane (1998–April 2011). Original data were abstracted where available and summarized on a separate Microsoft Excel (2007) database for analysis. A total of 14 studies comparative and non-comparative were identified and included.

RESULTS: The non-comparative and comparative data suggested that women with PCOS were more likely to develop EC. A meta-analyses of five comparative studies showed an increased risk of EC in women with an odds ratio of 2.89 with a 95% confidence interval of 1.52–5.48.

CONCLUSIONS: Women with PCOS are about three times more likely to develop EC compared with women without it. This translates into a 9% lifetime risk of EC in Caucasian women with PCOS compared with 3% in women without it. Although most women (91%) with PCOS will not develop endometrial cancer, our study has shown that they are more likely at increased risk. More studies are required to clarify the exact molecular mechanisms, determine the best way of screening and preventing disease progression.

Key words: polycystic ovary syndrome / PCOS / endometrial cancer / systematic review

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disease affecting women of reproductive age of whom ~5–10% have the syndrome**.** The aetiology is uncertain and because of its heterogeneity different groups classify PCOS differently. In 2003, an international consensus group proposed that PCOS should be diagnosed in women with at least two of the following present: oligomenorrhea or amenorrhea, hyperandrogenemia and polycystic ovaries defined by ultrasonography after exclusion of other medical conditions that cause irregular menstrual cycles and androgen excess (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003). Endometrial cancer (EC) is the most common female genital tract malignancy in most countries affecting 2–3% of women (mostly post-menopausal; Parker *et al.*, 1997; National Cancer Institute of Canada, 2003). Usually, the prognosis of EC is good with an overall survival rate of 80% because the majority of cases are diagnosed at an early stage (Markman, 2005). There are two major histological types of EC: Type I or endometrioid endometrial cancer (EEC), accounting for >75% of EC cases and Type 2, non-EEC (Sherman, 2000). There is currently no effective screening programme for EC and, in the UK, cases are mostly diagnosed following investigations including transvaginal ultrasound, pipelle biopsy and hysteroscopy in women who present most commonly with bleeding per vaginum (intermenstrual, post-menopausal or heavy menstrual).

Women with PCOS have several risk factors for EC and may be at increased risk of developing EC (Hardiman *et al.*, 2003). Some of the clinical, metabolic and molecular risk factors include unopposed estrogen stimulation of the endometrium in anovulatory PCOS women, obesity, insulin resistance, insulin like growth factors, diabetes, nulliparity, Cyclin D1, gluthathione-*S*-transferase and progesterone resistance (Hardiman *et al.*, 2003; Pillay *et al.*, 2006; Atiomo *et al.*, 2009). The exact strength of the association between PCOS and EC is however unclear and an article published in the *Lancet* in 2003 (Hardiman *et al.*, 2003) concluded that the evidence for an increased risk of endometrial carcinoma in PCOS was incomplete and contradictory. However, a recently published systematic review (Chittenden *et al.*, 2009) showed in a meta-analysis that women with PCOS were

almost three times more likely to develop EC with an odds ratio (OR) of 2.70 and a confidence interval (CI) of 1–7.29 (no difference to a 7.29 increased risk). A closer inspection of the data used in the meta-analysis however revealed that the 95% CIs of the ORs of three of the four studies used in the meta-analysis crossed 1 (no evidence of an effect) and the effect size of the published aggregated OR (2.70) of increased EC risk in women with PCOS was because of one case–control study of 399 women with newly diagnosed EC compared with 3040 controls (Escobedo et al., 1991) in which the OR for EC was 4.2 (95% CI: 1.7–10.4) in women with infertility associated with 'ovarian' factors. These data therefore suggested that there was still some uncertainty about the exact strength of the association between EC and PCOS.

The aim of this study therefore was to further investigate the exact strength of the association between PCOS and EC by carrying out an updated and independent systematic review and meta-analysis. This was thought to be an important research question because of the implications for clinical management and research including the need to incorporate clear surveillance and clinical prevention strategies for EC in women with PCOS was found to be at increased risk.

Materials and Methods

Studies eligible for review

Studies were eligible if they were retrospective or prospective, case–control cohort studies, cross-sectional or randomized controlled studies containing original data on association between PCOS and endometrial hyperplasia and carcinoma. Meta-analysis was performed on case–control cohort or cross-sectional studies.

Finding relevant studies

A literature search was carried out by two independent reviewers on major electronic databases: Medline 1996 to April 2011, EMBASE 1980 to April 2011and Cochrane Database of Systematic Reviews 1998 to April 2011. The keywords used to capture all potentially relevant studies were ' PCOS', 'PCO', 'polycystic ovary syndrome' or 'Stein–Leventhal syndrome' with 'endometrial carcinoma', 'EC' or 'endometrial hyperplasia'. Only articles published in English were retrieved. In addition, hand searching the abstracts of recent PCOS conferences and the references of all studies meeting the reference criteria were also carried out. All studies obtained as a result of the search were reviewed. The original PDFs of studies obtained from the search were located through direct online links to the files from the search results.

Data abstraction

Data extraction was carried out independently by two investigators, Z.H. and M.S. Studies where the outcomes included the incidence or prevalence of EC and in women with PCOS were included. In order to evaluate the strength of the association between PCOS and endometrial cancer in these women, all the data relating to diagnosis, prevention and treatment were extracted for analysis.

Studies identified from the different databases were initially saved separately on Microsoft Excel 2007. These results were then merged and sorted to enable the identification and removal of duplicated search results. Full articles and abstracts derived as a result of the search were read, and original data were abstracted where available and summarized on a separate database.

Statistics and data analysis

A note was made of the total number of studies identified and excluded either due to duplication or following review of the abstracts. A meta-analysis was performed on the comparative studies and an OR established. Test of heterogeneity using I^2 value was used to measure the extent of inconsistency among results. The higher the value is, the bigger the heterogeneity is. The statistical test for overall effect size was defined using the probability (P) value. A funnel plot of comparison of studies was used to assess publication bias (Fig. 1).

Results

Out of a total of 265 studies initially identified, 219 were excluded either due to duplication or following review of the abstracts. A total of 46 papers on the association of PCOS with endometrial hyperplasia/carcinoma were therefore included for thorough review. After detailed review, all review articles and those that were not in English were excluded. A total of 14 studies comparative and non-comparative studies were identified (Fig. 2) of which five comparative studies (studies with a control group) were eligible for use in the meta-analysis. Observational studies without a control arm, studies with no data on EC prevalence specifically presented for PCOS women and retrospective cross-sectional studies were excluded from the meta-analysis.

Data from five studies were used in the updated meta-analysis with a total of 4605 women Table I. Of these, 88 women had PCOS of whom 47 had EC and 4517 did not have PCOS of whom 773 had endometrial cancer. Escobedo et al. (1991) utilized data from the Cancer and Steroid Hormone Study. The subject group comprised women between the ages of 20 and 54 years with newly diagnosed endometrial cancer. The control groups were from the same age range selected by random-digit telephone dialling from the same geographic area where cancer patients resided. They identified PCOS based upon patient recall of the diagnosis being given to them by a physician. Niwa et al. (2000) in a case–control study selected 136 women with histologically proven EC. The age range was 40–70 years. The control group consisted of 376 healthy women who were randomly selected from the same population as the cases. They were sampled from healthy women attending a health promotion centre. PCOS was diagnosed by a physician. Pillay et al. (2006), looked at the prevalence of polycystic ovaries (PCOs), as a marker of PCOS and was investigated in ovarian sections from 128 women with EC (EC) and 83 women in the control group with benign gynaecological conditions. PCOS was diagnosed based on histological criteria. Iatrakis et al. (2006), included a group of women with a mean age of 46.3 years diagnosed with histologically EC. The control group was randomly selected from women between the ages of 43 and 48 years attending the gynaecology clinic without any EC diagnoses. PCOS was diagnosed by a physician. In the study by Fearnley et al. (2010), data came from a national population-based case–control study in Australia in which 156 cases with histologically confirmed newly diagnosed EC were identified and 398 controls were randomly selected from the national electoral roll. PCOS was diagnosed based on self-reported diagnosis.

Analysis of the aggregated data showed that the odds of developing EC was almost three times higher in women with PCOS as compared with women without PCOS (Fig. 3) with the CIs clearly >1 (OR: 2.89,

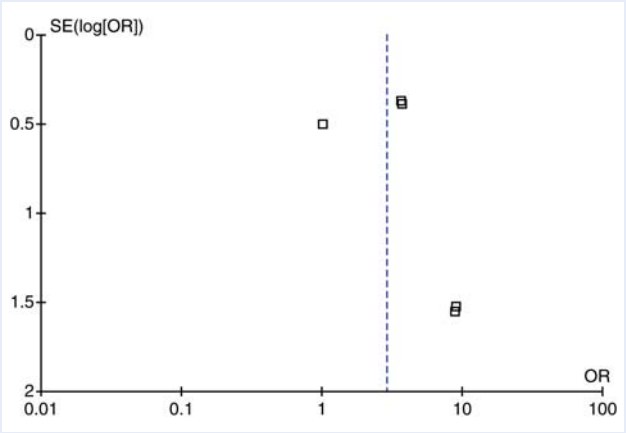

Figure 1 Funnel plot of comparison: 1 endometrial hyperplasia/cancer, outcome: 1.1 association between PCOS and endometrial hyperplasia/cancer.

95% CI: 1.52–5.48). Given that the background risk of developing EC in Caucasian women is somewhere in the order of a 3% lifetime risk (McCann *et al*., 2000; Greenlee *et al*., 2001) this would give an absolute lifetime risk of EC of ~9% in women with PCOS.

It was not possible to determine the exact strength of the association between PCOS and EC from the nine studies (Speert, 1949; Dockerty *et al*., 1951; Jackson and Dockerty, 1957; Ramzy and Nisker, 1979; Coulam *et al*., 1983; Gallup and Stock, 1984; Dahlgren *et al*., 1991; Ho *et al*., 1997; Wild *et al*., 2000) excluded from the meta-analysis, although PCOS was thought to be linked with EC in most of these studies.

Discussion

This is the first systematic review and meta-analysis to have demonstrated an unambiguous link between PCOS and EC. The data used in the previously published meta-analysis (Chittenden *et al*., 2009) revealed that the 95% CIs of the ORs of three of the four studies used in the meta-analysis crossed 1 (no evidence of an effect) and the effect size of the published aggregated OR (2.70) of increased

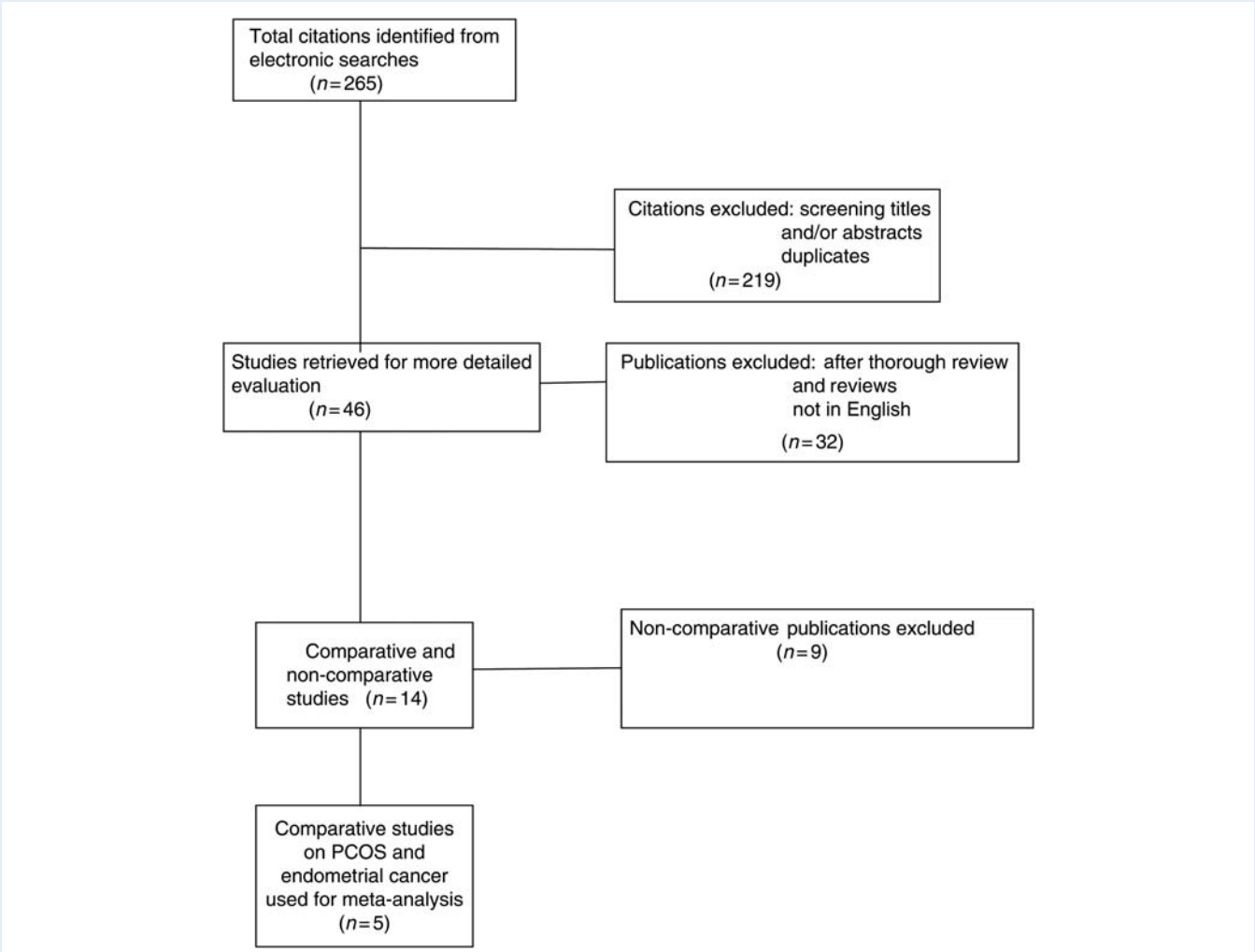

Figure 2 Study selection process for systematic review of PCOS and endometrial cancer.

Table I Characteristics studies investigating an association between PCOS and EC included in the meta-analysis.

Authors	Methodology	Participants	Findings	Comments
Escobedo et al. (1991)	Case–control	399 cases of endometrial carcinoma; 3040 controls	OR for endometrial carcinoma of 4.2 for 'ovarian factor' infertility	No data for women with PCOS
Niwa et al. (2000)	Case–control	136 histologically confirmed endometrial carcinoma (EC); 376 controls	Higher frequency of EC in a group of PCOS <40 years	No significant risk
Iatrakis et al. (2006)	Case–control	81 histologically confirmed endometrial carcinoma	Higher frequency in PCOS women <50 years	No significant risk
Pillay et al. (2006)	Cross-sectional retrospective	128 histologically confirmed endometrial carcinoma; 83 controls	Prevalence higher in the PCOS group <50 years of age	Evidence of association
Fearnley et al. (2010)	Case–control	156 histologically confirmed endometrial carcinoma; 398 controls	4-fold increased risk of endometrial carcinoma in PCOS women	Evidence of association

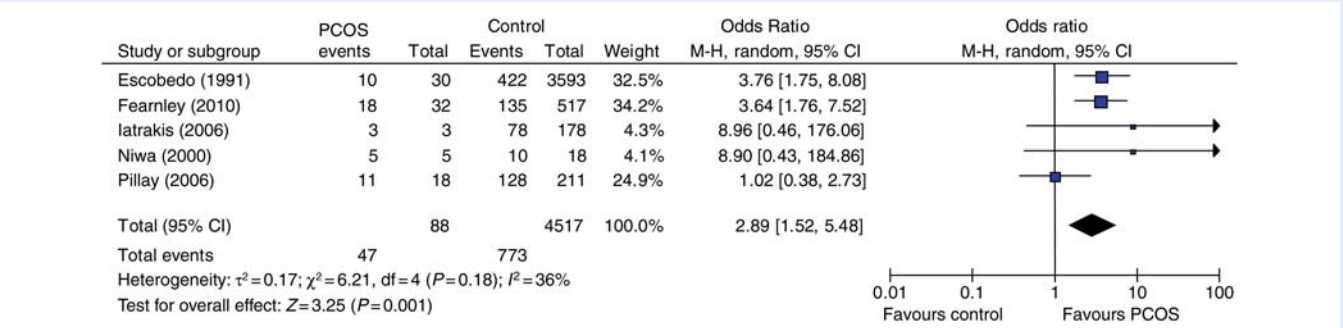

Figure 3 Meta-analyses of EC risk in women with PCOS.

EC risk in women with PCOS was because of one case–control study of 399 women with newly diagnosed EC compared with 3040 controls (Escobedo et al., 1991) in which the OR for EC was 4.2 (95% CI: 1.7–10.4) in women with infertility associated with 'ovarian' factors. In our paper, this meta-analysis has been boosted by data from a large Australian study (Fearnley et al., 2010) and it showed that women with PCOS were found to have a 3-fold risk of developing EC compared with controls with 95% CIs clearly >1. This translates into a 9% lifetime risk of EC in Caucasian women with PCOS compared with 3% in women without it. The study also confirmed that although PCOS was first suggested as a risk factor for EC >60 years ago (Speert, 1949), in a study where an increased incidence of cystic ovaries in young women with EC was noted, the exact strength of this association has never been clear (Hardiman et al., 2003;Chittenden et al., 2009).

Several uncontrolled or retrospective cohort studies to the first study suggesting a link between PCOS and EC (Speert, 1949) either did not demonstrate a link (Jackson and Dockerty, 1957; Ramzy and Nisker, 1979; Ho et al., 1997), or reported data which was not suitable for inclusion in a meta-analysis (Dockerty et al., 1951; Coulam et al., 1983; Gallup and Stock, 1984; Dahlgren et al., 1991; Wild et al., 2000). For example, Dockerty et al. (1951) in their case series of young women with endometrial carcinoma noted a high incidence of associated fibromyoma, myohypertrophy and endometrial hyperplasia, which were thought to indicate 'chronic hyperestrogenism' but the study was uncontrolled. In another example, Jackson and Dockerty (1957) described 43 patients with Stein–Leventhal syndrome (PCOS) and 16 of these women were identified by examining surgical specimens removed from a group of 'several thousand patients' with EC. The remaining 27 patients were women with symptoms of the Stein–Leventhal syndrome and a confirmatory ovarian biopsy. Endometrial tissue was available for examination in only 15 of these cases. Thirteen samples showed 'thickening', 2 were atrophic, but there were no reported cases of endometrial carcinoma. Nevertheless, Jackson and Dockerty concluded that their most important observation concerned the link between the Stein–Leventhal syndrome (PCOS) and endometrial carcinoma.

The main limitation of this study was the diagnosis of PCOS among the participants of the studies chosen for the meta-analysis, one of them (Escobedo et al., 1991) was published before the first NIH consensus on PCOS definition; in the other two studies (Niwa et al., 2000; Iatrakis et al., 2006) PCOS participants were enrolled based on a diagnosis by a physician, without other specifications. In the study of Pillay et al. (2006), PCOS women were characterized by the presence of PCOs on ovarian sections and Fearnley et al. (2010) characterized their PCOS participants based on self-reported diagnosis. These could have led to selection biases amongst PCOS women.

A large proportion of the studies identified in the literature search also either had small patient groups or did not have control groups, which limited the number of studies eligible for meta-analysis. The published OR EC risk in PCOS in one study (Fearnley et al., 2010)

was 4.0 (95% CI: 1.7–9.3; unadjusted for BMI) which was different from the OR we calculated [3.76 (95% CI: 1.76–7.52)] for their study and used in our meta-analysis based on the primary data presented in the paper. We attempted to make contact with the authors to clarify this minor discrepancy in the data with no success. We however did not think the magnitude of difference was significant. In addition, of two of the studies used in the meta-analysis showed OR with 95% CI of <0.5 to >170.0 (Fig. 3), meaning that no significant risk could be determined.

In conclusion, this study showed that women with PCOS had an OR of developing EC of 2.89 with a 95% CI of 1.52–5.48. This almost 3-fold risk of EC in women with PCOS translates into a lifetime risk of 9% given the background lifetime risk of EC in the general population of 3%. Although most women with PCOS (91%) will not develop EC, our study has shown that they are more likely at increased risk. This finding strengthens evidence base in support of link between PCOS and EC. It has relevant implications for clinical practice as it calls for the implementation of risk-reducing measures including the potential of introducing a screening programme for early cancer detection as treatment of EC at an early stage is associated with an excellent 86% 5-year survival rate. What seems indispensable for proper evaluation of this issue is the need for further studies to clarify the question of the association between EC and PCOS such as large follow-up prospective population studies with clearly defined cases, controls and study outcomes/end-points that will enable clinicians to draw firmer conclusions and improve the care of women with PCOS.

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Authors' roles

Z.H. and M.S. contributed to design and acquisition of data, drafting of article and final approval of versions to be published. W.A. contributed to design and interpretation of data, drafting of article and final approval of versions to be published.

Details of ethics approval

Not applicable as this study did not involve direct patient intervention.

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Conflict of interest

None declared.

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