Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis

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Objective: To perform a systematic review and meta-analysis of studies that compared the prevalence of anxiety symptoms in women with polycystic ovary syndrome (PCOS) and control women.
Design: Meta-analysis and systematic review.
Setting: University practice.
Patient(s): Cross-sectional studies comparing PCOS subjects and geographically matched clearly defined non-PCOS control subjects with data on age and body mass index (BMI).
Intervention(s): Anxiety screening tool.
Main Outcome Measure(s): The primary analysis contrasted prevalence of anxiety. Cochrane Review Manager 5.0.24 software was used to construct forest plots comparing frequency of anxiety symptoms in case and control subjects.
Result(s): Of 613 screened articles, nine met our selection criteria for a systematic review and four were included in the meta-analysis. The prevalence of generalized anxiety symptoms was available in four studies and was significantly greater in PCOS subjects (42/206, 20.4%) compared to controls (8/204, 3.9%). The odds for anxiety symptoms were significantly greater in women with PCOS compared with control subjects (odds ratio 6.88, 95% confidence interval 2.5–18.9). The mean anxiety score was significantly increased in three of the remaining five studies. Other anxiety disorders, such as social phobia, panic attacks, and obsessive compulsive disorders, were assessed infrequently.
Conclusion(s): Our systematic review suggests an increased odds of anxiety symptoms in women with PCOS, underscoring the importance of screening all women with PCOS for anxiety symptoms. Follow-up evaluation and treatment are essential, because generalized anxiety disorder is a chronic condition. Potential contributors for anxiety symptoms, such as hirsutism, obesity, and/or infertility may be specific to women with PCOS but need further investigation. (Fertil Steril® 2012;97:225–30. ©2012 by American Society for Reproductive Medicine.)
Key Words: PCOS, anxiety disorder, meta-analysis

Polycystic ovary syndrome is a common endocrine disorder in adolescents and reproductive-age women. The classic features include menstrual irregularity, biochemical or clinical hyperandrogenism, and ultrasound appearance of polycystic ovaries (1). Insulin resistance is one of the underlying mechanisms for the metabolic manifestations of this syndrome, which include increased risk for obesity, dyslipidemia, glucose intolerance, and long-term cardiovascular disease (CVD). Depression and anxiety disorders are also recognized risk factors for CVD. Recently, in a systematic review and meta-analysis, we found that women with PCOS had a fourfold greater odds of depressive symptoms compared with age-matched control women (2). Further subanalysis of body mass index (BMI)–matched subjects also demonstrated greater odds of depressive symptoms in women with PCOS. We have previously examined the risk of depression in PCOS and found a persistent high prevalence of depression after 12–18 months (3).

Mood disorders are commonly associated with anxiety disorders, especially generalized anxiety disorder (GAD) (4). The estimated prevalence of anxiety disorders is 5%–8% in women seen in the primary care setting. Diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) for GAD include excessive anxiety and worry about a number of events or activities, occurring more days than not for $\geq$6 months, out of proportion to the likelihood or impact of feared events. We have previously reported that more women with PCOS (14%) compared with control women (1%) had anxiety symptoms (5). Abnormal or inappropriate anxiety can become a problem when it occurs without any recognizable stimulus or when the

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stimulus does not warrant such a reaction. Often, anxiety gets generalized to other situations, and can then become overwhelming or associated with life in general. Typically, GAD develops over a period of time and may not be noticed until it is significant enough to cause problems with functioning. In the National Comorbidity Survey, patients with GAD had a high prevalence of social phobia, specific phobia, panic disorder, and major depression (6, 7). The majority of people with GAD reported substantial interference with their life, a high degree of professional help seeking, and a high use of medication to relieve their symptoms. We performed a systematic analysis of the literature to determine the prevalence of anxiety symptoms in women with clearly defined PCOS women compared with well selected control women.

MATERIALS AND METHODS

We included only published articles with cross-sectional comparisons of women with PCOS and control women both screened for anxiety symptoms. Inclusion criteria were women who met the definition of PCOS based on National Institutes of Health (NIH) (8) or Rotterdam (9) criteria after excluding other endocrine and androgen excess disorders. Control subjects were recruited from the same catchment area as the women with PCOS either through the clinic population or advertising. Studies were excluded if age and BMI were not available for both groups. We included articles that used validated standard screening tools for assessing anxiety and applied them to both PCOS and control women. Review articles and internet surveys were not included. Three of the authors searched the articles (W.F., A.D., and R.W.) with the assistance of a research librarian (S.C.). Each article was independently assessed for inclusion and exclusion criteria and when disagreements occurred it was arbitrated by two-thirds agreement. Data were extracted from the text, tables, and graphs in the manuscripts and by contacting authors when data were not available in the paper. All data were abstracted and put into a table format in a systematic manner. The Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analyses and systematic reviews of observational studies were applied to this study.

Sources

Searches were conducted in the following databases: Medline (OvidSP; 1950–April 2011); Medline In-Process and Other Nonindexed Citations (OvidSP; April 2011); Embase Classic + Embase (OvidSP; 1947–April 2011); PsycInfo (OvidSP; 1806–April 2011); Current Contents–Clinical Medicine, Current Contents–Social and Behavioral Sciences, and Current Contents–Life Sciences (ISI Web of Knowledge; 1998–April 2011); Web of Science–Science Citation Index Expanded (ISI Web of Knowledge; 1899–April 2011); and Web of Science–Social Sciences Citation Index (ISI Web of Knowledge; 1898–April 2011). Articles published in languages other than English were included. Retrieval from Medline, Embase, and PsycInfo was limited to human studies.

Supplemental Table 1 (available online at www.fertstert.org) includes our search strategies detailing the special features, key words, and controlled vocabulary terms used. The search words included were: polycystic ovary syndrome, PCOS, polycystic ovary, and Stein Leventhal syndrome; and anxiety, anxiety disorders, anxious, panic, phobia, nervous. Data sets of experts in the field were queried recognizing positive publication bias, and bibliographies of pertinent original and review articles were searched for additional references published by April 2011. Duplicate publications that were updates of earlier data sets were excluded.

Statistical Analysis

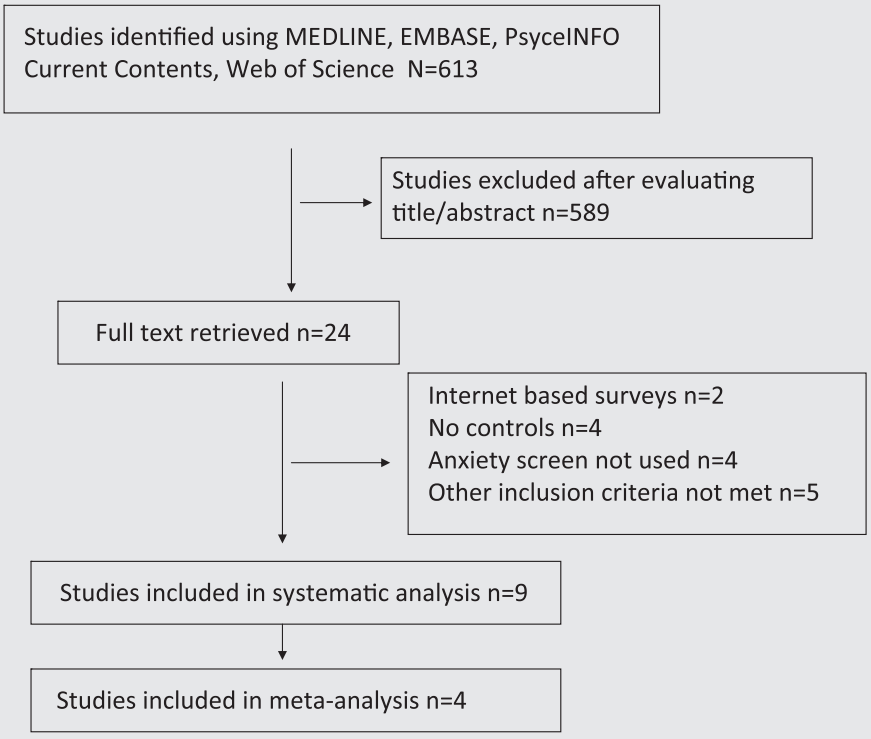
The primary analysis was the meta-analysis of studies to estimate the pooled odds of abnormal anxiety scores in women with PCOS compared with control women. Cochrane Review Manager 5.0.24 software was used to construct forest plots comparing prevalence of anxiety in PCOS and control subjects, reporting the more conservative random effects models. τ^2, χ^2, and I^2 tests of heterogeneity were applied. Studies that fulfilled our inclusion criteria but reported mean depression scores only were included in the systematic review but not in the meta-analysis. Means were compared with the Student t test and medians with the Wilcoxon-Mann-Whitney U test.

RESULTS

A total of 613 articles were identified. Figure 1 demonstrates the flow for articles selection. Twenty-four articles were evaluated in detail, and a total of nine studies (2004–2010) met our inclusion criteria. Seven studies used the Rotterdam criteria and two used the NIH criteria for the diagnosis of PCOS (Table 1). All of the studies screened clinic populations, except one that used an in-depth telephone screening tool to confirm previous physician-established diagnosis of PCOS (10). All of the studies screened adults with PCOS and reported their educational level, marital status, and parity, except one that screened only adolescents (11). The majority of PCOS and control subjects were overweight and obese. The quality assessment of the studies included in the systematic review and meta-analysis is presented in Supplemental Table 2 (available online at www.fertstert.org). The commonest screening tool used was the State-Trait Anxiety Inventory. The other validated screening tools used are listed in Table 2.

The prevalence of generalized anxiety symptoms was reported in four studies and was significantly higher in PCOS subjects (Table 2). Figure 2 demonstrates the pooled odds of generalized anxiety symptoms in women with PCOS (odds ratio [OR] 6.88, 95% confidence interval [CI] 2.5–18.9; $P=.002$) compared with control women. For the random effects model, χ^2 analysis for heterogeneity was not significant ($P=.27$; Fig. 2). One of the studies was matched for both age and BMI and observed a high odds for anxiety in PCOS women (OR 13 95%, CI 1.95–552.4; $P=.002$) (12). There was no difference in marital status, employment status, and parity between the two groups in three studies (5, 12, 13), and these parameters were not reported in the other study (10). Of the five studies that reported mean anxiety scores, three had significantly higher anxiety scores in PCOS women compared with control women (Table 2) (11, 14, 15). In all

FIGURE 1



Flow chart for systematic review and meta-analysis.

Dokras. Increased prevalence of anxiety in PCOS. Fertil Steril 2012.

three studies there was no significant difference in age and BMI between the two groups.

Only a few studies reported other types of anxiety disorders besides GAD, such as social phobia (12, 13, 16), obsessive compulsive disorder (OCD) (13, 16), and panic disorders (12, 13) (Table 2). Two of three studies found higher prevalence of social phobia in women with PCOS (12, 13). One of two studies reported a higher prevalence of OCD (16). Overall, three studies reported follow-up evaluation by a psychiatrist after the initial screening (5, 11, 13).

DISCUSSION

Anxiety symptoms are common in the general female population, occur at an early age, and coexist with other mood disorders such as depression. Health-related quality of life surveys suggest that women with PCOS may be at an increased risk for anxiety symptoms, given their low self-esteem, poor body image, fear of future health problems, including infertility, and perceived lack of effective treatment. There are limited data on the prevalence of anxiety disorders estimated using validated anxiety screening tools in women with PCOS. We conducted a systematic analysis of the literature and found an increased prevalence of generalized anxiety and an increase in mean anxiety scores in women with PCOS compared with control women. Because the prevalence of anxiety disorders varies between North America and western Europe (7), we included studies from a number of countries with geographically matched controls. A variety of validated screening tools were used in the studies reporting the higher prevalence of anxiety symptoms. A few of these studies also examined the prevalence of other anxiety disorders, including panic disorder, social phobia, and obsessive compulsive disorder. Although the number of published studies is currently small, collectively they suggest that the anxiety symptom burden may be more prevalent in women with PCOS.

Anxiety disorders commonly have an early onset in adolescence, and longitudinal studies in the general population have described anxiety as a chronic recurring condition (17). There are limited data in the literature assessing prevalence of anxiety symptoms in adolescents with PCOS. Only one study specifically examined anxiety and depression scores in that population: Laggari et al. (11) used the State-Trait Anxiety Inventory to screen subjects and, after controlling for age, socioeconomic status, and stressful life events, reported a slight increase in anxiety scores in PCOS girls (OR 1.08, 95% CI 1.003–1.17). Given that anxiety is a chronic recurring disorder, it has been suggested that appropriate evaluation and treatment of anxiety symptoms at an early age may prevent the onset of secondary disorders (18). Some authors have suggested that adolescents with PCOS are at a higher risk for anxiety symptoms likely related to the clinical signs of hyperandrogenism. In a study of hirsute girls aged 13–18 years, anxiety was diagnosed in 26% compared with 10% in the control (nonhirsute) girls (19). That study also showed decreased scores for quality of life and self-esteem in the hirsute girls. Successful treatment of hirsutism has been shown to be associated with improvement in

TABLE 1

Demographics of studies included in systematic review and meta-analysis.

Study	PCOS diagnosis criteria	Country	n		Age (y, mean ± SE)		BMI (kg/m^2, mean ± SE)		Previous psychiatric illness	Current medications	Education level	Marital status
			PCOS	Control	PCOS	Control	PCOS	Control				
Moran et al., 2010	Rotterdam	Australia	24	22	22.4 ± 0.39	21.9 ± 0.47	29.1 ± 1.5**	22.0 ± 0.8	Excluded	NA	NA	NA
Jedel et al., 2010	Rotterdam	Sweden	30	30	28 (median)	27.8 (median)	25 ± 8	25 ± 10	Excluded	Excluded	ND	ND
Mansson et al., 2008	Rotterdam	Sweden	49	49	35.9 ± 10.4	35.9 ± 10.4	29 ± 7**	23.5 ± 3	NA	OCP: ND; anxiolytic drugs: higher use in PCOS	ND	ND
Hollinrake et al., 2007	Rotterdam	USA	103	103	29.8 ± 6.2	30.7 ± 6.5	35 ± 9*	25 ± 5	NA	OCP: ND; metformin: ND; antidepressant: higher use in PCOS	ND	ND
Soyupek et al., 2010	Rotterdam	Turkey	40	39	26.1 ± 6.1	26.1 ± 5.6	24.2 ± 5.6	21.8 ± 3.8	NA	NA	NA	NA
Laggari et al., 2009	Rotterdam	Greece	22	22	17 ± 2.2	17 ± 2	25 ± 6	21 ± 3	NA	NA	ND	NA
Ozenli et al., 2008	Rotterdam	Turkey	35	35	27.6 ± 7.7	26.5 ± 5.2	25.4 ± 5.5	24.8 ± 5.4	NA	Excluded	ND	ND
Hahn et al., 2005	NIH	Germany	120	50	29 ± 5.4	30 ± 5.7	31 ± 9**	24 ± 5.3	NA	Excluded	ND	ND
Weiner et al., 2004	NIH	USA	27	27	28.1 ± 6.5	30.1 ± 6.4	38 ± 8	37 ± 7	Excluded	Excluded	ND	ND

Note: NA = data not available; ND = data not significantly different.
* $P<.05$.
** $P<.01$.

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anxiety scores in adult women with PCOS. In a randomized controlled 6-month study comparing different laser treatments, women with PCOS reported significant improvements in both depression and anxiety scores (20). There are very few studies examining the relationship between hyperandrogenism and anxiety symptoms in women with PCOS. Recently, a large study showed that total and free testosterone levels or clinical signs of hyperandrogenism did not correlate with anxiety symptoms (21). In the present meta-analysis, social phobia correlated with free androgen index (13), state anxiety correlated with free testosterone levels in another study (22), but in a third study hirsutism scores did not correlate with the Revised Symptom Checklist 90 scale (16). Larger studies are needed to better evaluate the relationship between both clinical or biochemical attributes of hyperandrogenism and anxiety symptoms in women with PCOS.

The association between anxiety symptoms and BMI is less well established compared with the association between depression and BMI. Given the small number of studies included in the meta-analysis, we were unable to perform a subanalysis of BMI-matched studies. BMI correlated with anxiety scores in some studies (10, 13) but not in others (16). One study included age- and BMI-matched subjects and reported a higher prevalence of generalized anxiety and phobias in women with PCOS (12). In four other studies with no significant difference in BMI between PCOS and control subjects, the anxiety scores were significantly higher in three (11, 14, 15). Another potential factor that may contribute to anxiety symptoms in women with PCOS is an unfulfilled wish to conceive. Hahn et al. (16) reported a higher prevalence of infertility in PCOS compared with control subjects. However, they did not find any differences in psychosocial variables between subjects with infertility compared with those who had conceived. Another study excluded subjects with current infertility and reported higher mean anxiety scores in women with PCOS (15). In that study (n = 70), there were no differences in age, BMI, marital status, employment, and gravidity between the two groups. It has been suggested that the diagnosis of infertility or use of infertility treatments may result in depressive or anxiety symptoms but not in a clinically significant disorder (13).

Overall, our review found that relatively few studies addressed anxiety in women with PCOS, although anxiety disorders constitute the most common psychiatric diagnoses among endocrine patients and in the population in general. Only three studies described follow-up evaluation of these subjects (5, 11, 13). In some of the studies the mean anxiety scores were relatively, low suggesting that a psychiatric diagnosis according to DSM-IV criteria may not have been confirmed at the time of psychiatric follow-up. This underscores the need for longitudinal follow-up and an appropriate evaluation of underlying etiology for anxiety symptoms in these subjects. There are very few longitudinal studies examining the progression of mood disorders in women with PCOS. We have previously reported a high prevalence for increased anxiety scores in women with PCOS compared with control women (5). In a follow-up study of the same group of subjects we reported a similar prevalence of persistent anxiety symptoms (15%) (3). During the interval, the two symptoms that

TABLE 2

Systematic review of studies with anxiety scores in women with PCOS and control women.

	Abnormal anxiety scores (%)		Anxiety scores (mean ± SE)		
Study	**PCOS**	**Control**	**PCOS**	**Control**	**Anxiety screening tool**
Moran et al., 2010	37.5*	9.1			HADS, moderate anxiety
Jedel et al., 2010	63**	13			BSA-S: sum total ≥11
	13**	2			Phobias
Mansson et al., 2008	13	2			MINI NPI, generalized anxiety disorder
	1	0			OCD
	10	8			Panic disorder
	27**	2			Social phobia
Hollinrake et al., 2007	14**	0.9			PRIME-MD, PHQ
Soyupek et al., 2010			3.2 ± 2.2**	1.9 ± 2.1	BAI >11
Laggari et al., 2009			36.5 ± 10.4*	31.5 ± 8.2	STAI-Gr
Ozenli et al., 2008			47.8 ± 8.1**	42.5 ± 5.5	STAI
Hahn et al., 2005			0.57 ± 0.61	0.40 ± 0.60	SCL-90-R: anxiety
			0.75 ± 0.66**	0.44 ± 0.46	OCD
			0.31 ± 0.56	0.22 ± 0.54	Phobia
Weiner et al., 2004			37.67 ± 12.42	32.56 ± 7.61	STAI: state anxiety
			43.89 ± 11.68	37.81 ± 8.94	STAI: trait anxiety

Note: BAI = Beck Anxiety Inventory; BSA-S = Brief Scale for Anxiety; HADS = Hospital Anxiety and Depression Scale; MINI NPI = Mini Neuropsychiatric Interview; OCD = obsessive compulsive disorder; PRIME-MD PHQ = Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; SCL-90-R = Revised Symptom Checklist 90 (German version); STAI = State-Trait Anxiety Inventory; STAI-gr = Greek version of STAI.

* $P<.05$.

** $P<.01$.

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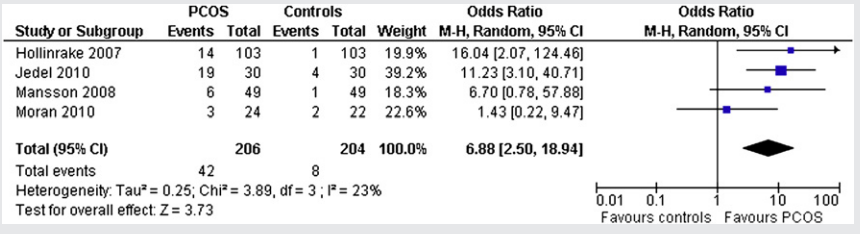
markedly improved were menstrual irregularity and acne, most likely owing to treatment with combination hormonal contraceptives. Of further importance is understanding the impact of specific factors associated with PCOS that may be associated with reducing anxiety in this population.

Known risk factors for GAD include family history, stressful life events, and physical or emotional childhood abuse. Some authors have speculated that unique factors may be related to anxiety symptoms in PCOS: low self-esteem, poor body image (especially weight) (10), fear of future health, including infertility (23), and clinical hyperandrogenism, including acne and hirsutism (22). In a large internet-based survey (not included in our analysis), anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) in 448 PCOS women (24). Of interest, 34% of the PCOS women had clinically relevant increased HADS anxiety scores, and their quality of life was significantly impaired ($P<.001$). Clinically relevant HADS anxiety scores were more common in PCOS women with acne (OR 1.52, 95% CI 1.03–2.52) and an unfulfilled wish to conceive (OR 1.50, 95% CI 1.01–2.23). Other anxiety disorders that tend to coexist with GAD may also be associated with the above risk factors. Two studies have demonstrated an increased prevalence of social phobia in women with PCOS (12, 13). The authors suggest that social phobia may be triggered by reactions from other people toward obesity and hirsutism, because BMI and free androgen index were higher in PCOS women who reported social phobia (13). If this relationship with anxiety symptoms is significant in women with PCOS, then effective interventions might include patient education about PCOS and its long-term impact, successful implementation of early improved lifestyle changes, and treatment of acne and hirsutism.

In the general population, 35%–50% of individuals with major depression meet criteria for GAD (4). Coexisting GAD in depressed patients may worsen the outcome by increasing the risk of suicide, worsening overall symptoms, conferring a poorer response to treatment, increasing the number of medically unexplained symptoms, and increasing functional disability. The risk of developing coexistent depression and anxiety in women with PCOS is unknown. In seven of the studies included in our systematic review the subjects were

FIGURE 2



Forest plot including 4 studies comparing risk of anxiety in women with PCOS compared to controls.

Dokras. Increased prevalence of anxiety in PCOS. Fertil Steril 2012.

also screened for depression, and in six of those studies the prevalence of abnormal depression scores was significantly higher than in the control women. Untreated GAD is also associated with high rates of medical comorbidity and increased utilization of medical health care (25). The burden of health care costs related to PCOS is known to be high, and these estimates did not include costs related to mood and anxiety disorders, which are known to be considerable (26).

Recently, another meta-analysis was published examining the prevalence of depression and anxiety symptoms in women with PCOS (27). That meta-analysis concurred with our previous systematic review and meta-analysis, which reported that women with PCOS had a higher odds of depressive symptoms compared to age-matched control women (4). Those authors also reported the odds of anxiety symptoms to be higher in women with PCOS compared with control women ($P<.01$; six studies). In the present study, we had different inclusion criteria (e.g., no internet surveys), thereby including five additional studies that were not part of the meta-analysis published by Barry et al. (27). The limitations of the present review include small study size and possibility of publication bias. In addition, most of the published studies are cross-sectional and not designed to determine causality.

In summary, published studies indicate that women with PCOS may have a higher prevalence of anxiety symptoms compared with control women. Our meta-analysis also suggests that more studies are needed to clearly define the prevalence of anxiety disorders in adolescents with PCOS, given the early age of onset and chronic recurring nature of anxiety disorders. Adult women with PCOS should be routinely screened for anxiety and mood disorders using validated screening tools and referred for appropriate evaluation and/or use of psychologic and pharmacologic treatments. Future studies should be aimed at evaluating the association of common PCOS-specific characteristics, such as hyperandrogenism and infertility, with anxiety symptoms and disorders. This will help us to better understand why anxiety is more prevalent in women with PCOS and thereby to individualize therapies.

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SUPPLEMENTAL TABLE 1

Search strategy with MeSH terms.

1	Ovary Polycystic Disease/
2	pcos.mp.
3	(polycyst$ ovar$ or ovar$ polycyst$).mp.
4	Stein Leventhal Syndrome/
5	stein leventhal$.mp.
6	or/1-5
7	Anxiety/
8	exp Anxiety Disorder/
9	(anxiet$ or anxious$).mp.
10	(panic$ or phobi$ or nervous$).mp.
11	or/7-10
12	6 and 11
13	..l/12 hu=y
14	..l/13 yr=2005-2011
15	13 not 14

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SUPPLEMENTAL TABLE 2

Assessment of studies included in systematic review and meta-analysis, using the Newcastle-Ottawa Assessment Scale.

Study	Case definition adequate	Representativeness of case subjects	Selection of control subjects	Definition of control subjects	Comparability of case and control subjects	Ascertainment of exposure	Nonresponse rate
Moran et al., 2010	X	X	*	*	*	**	*
Jedel et al., 2010	*	*	*	*	*	**	*
Mansson et al., 2008	*	*	*	*	*	**	*
Hollinrake et al., 2007	*	*	X	*	**	**	*
Soyupek et al., 2010	*	*	X	*	**	**	*
Laggari et al., 2009	*	*	*	*	**	**	*
Ozenli et al., 2008	*	*	*	*	**	**	*
Hahn et al., 2005	*	*	*	*	**	**	*
Weiner et al., 2004	*	*	*	*	**	**	*

Note: Selection: 1) Is the case definition adequate? (a) yes, with independent validation (*), (b) yes, e.g., record linkage or based on self-reports, (c) no description; 2) representativeness of case subjects: (a) consecutive or obviously representative series of cases (*), (b) potential for selection biases or not stated; 3) selection of control subjects: (a) community control subjects (*), (b) hospital control subjects, (c) no description; 4) definition of controls: (a) no history of disease (end point) (*), (b) no description of source. Comparability: comparability of case and control subjects on basis of design or analysis: (a) study control subjects for age (most important factor) (*), (b) study control subjects for any additional factor (BMI) (*) (could be modified to indicate specific control for a second factor). Exposure: 1) ascertainment of exposure: (a) secure record (e.g., surgical records) (*), (b) structured interview where blind to case/control status (*), (c) interview not blinded to case/control status, (d) written self-report or medical record only, (e) no description; 2) same method of ascertainment for case and control subjects: (a) yes (*), (b) no; 3) nonresponse rate: (a) same rate for both groups (*), (b) nonrespondents described, (c) rate different and no designation.

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