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Polycystic ovary syndrome and risk of uterine leiomyomata

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Abstract

Objective—To examine the association between polycystic ovary syndrome (PCOS) and the risk of uterine leiomyomata (UL).

Design—Prospective cohort study.

Setting—Participants from the Black Women's Health Study, an ongoing prospective cohort study of African-American women aged 21–69 years in 1995 residing in the United States. Participants completed mailed questionnaires about their health status every 2 years.

Patient(s)—Premenopausal women with no history of UL at the start of follow-up (N = 23,571).

Intervention(s)—No interventions were administered.

Main Outcome Measure—Incidence of UL among those with and without self-reported, physician-diagnosed PCOS over a 6-year period of follow-up (1997–2003). Medical-record validation in a random subset of UL cases confirmed 96% of diagnoses.

Result(s)—During 114,373 person-years of follow-up, 3,631 new cases of UL confirmed by ultrasound (N = 2,926) or hysterectomy (N = 705) were reported. After adjustment for potential confounders, the incidence of UL was 65% higher among women with PCOS than women without PCOS (incidence rate ratio, 1.65; 95% confidence interval, 1.21–2.24). The incidence rate ratios remained constant with increasing time after the diagnosis of PCOS. Results were similar when analyses were confined to women reporting a recent Papanicolaou smear, a proxy for a pelvic examination.

Conclusion(s)—The present study suggests a positive association between PCOS and UL in African-American women.

Keywords

Stein-Leventhal syndrome; polycystic ovaries; uterine neoplasms; leiomyoma; African-Americans; premenopausal; females

Polycystic ovary syndrome (PCOS) is a disease characterized by menstrual irregularity and androgen excess not attributable to another cause (1,2). A more comprehensive definition of PCOS arose at a 1990 National Institutes of Health (NIH) conference on the disorder (3), and was revised in 2003 (4). The 1990 NIH diagnostic criteria required that the patient have both

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chronic anovulation and clinical and/or biochemical signs of hyperandrogenism, and no evidence of other related disorders, such as hyperprolactenemia, thyroid disorders, or nonclassic adrenal hyperplasia (3). The revised 2003 criteria added ultrasound evidence of polycystic ovaries as a third criterion, and required that patients manifest 2 of the 3 criteria. While estimates of the prevalence of PCOS in the general population range from 2%–20%, depending on the definition used, a recent prospective study using the 1990 NIH criteria estimated the prevalence to be 3%–6% of reproductive-aged women (5,6). The prevalence did not differ markedly between black and white women (6).

Women with PCOS often have elevated LH levels (2), and are at higher risk for developing infertility, endometrial carcinoma, and a number of metabolic disorders, including insulin resistance, diabetes, hypertension, and cardiovascular disease (7–10). Whether PCOS is associated with an increased risk of uterine leiomyomata (UL) is unknown. Although UL are thought to be influenced primarily by endogenous levels of estrogens (Es) and P, there is a growing body of literature to suggest that elevated LH levels, independent of ovarian function (11–14), and dysregulation of the insulin-growth factor and growth hormone (IGF-GH) axis, may be important in the etiology of UL (15–19). The cross-sectional Uterine Fibroid Study of the National Institute of Environmental Health Sciences (NIEHS) found a positive association between urinary LH levels and risk of UL, particularly for large tumors (12). Other epidemiologic studies found the risk of UL to be positively associated with medication-treated diabetes (20) and hypertension (20,21), conditions that are associated with PCOS (9). Finally, PCOS was associated with a high ratio of E_2 to P(22), which may be an important mechanism by which PCOS affects the risk of UL. Thus, PCOS may influence the development of UL via elevation of LH levels, dys-regulation of the IGF-GH axis, and/or increased levels of unopposed estrogens.

With the use of data from the Black Women's Health Study (BWHS), a large prospective cohort study of African-American women, we evaluated the association between self-reported PCOS and UL.

MATERIALS AND METHODS

Study Population

The BWHS is an ongoing, prospective cohort study that was established in 1995. Approximately 59,000 African-American women aged 21– 69 years were enrolled through self-administered questionnaires mailed to subscribers of *Essence* magazine, members of black professional organizations, and friends and relatives of early respondents (23). The baseline questionnaire elicited information on demographic and behavioral characteristics, healthcare utilization, and medical conditions. Women who self-identified as "black" on their 1997 questionnaire were considered eligible for inclusion. The cohort is followed every 2 years by postal questionnaire, and >80% of the original cohort completed a questionnaire in each follow-up cycle. The study protocol was approved by the institutional review boards of Boston University Medical Center (Boston, Massachusetts) and Howard University Cancer Center (Washington, D.C.).

Follow-up for the incidence of UL began in 1997, the start of the second questionnaire cycle, because self-reported method of confirmation for UL was first elicited on the 1999 questionnaire. We restricted the sample to premenopausal women with intact uteri because UL are rare after menopause (24). Of the 53,176 women who completed the 1997 questionnaire, we therefore excluded women who reported natural menopause (N =5,193), hysterectomy without removal of both ovaries (N =6,685), bilateral oophorectomy with or without hysterectomy (N =4,259), medication-induced menopause (N = 42), or unknown menopausal status (N = 418) at the start of follow-up. Women who reported a diagnosis of UL before 1997

(N = 10,502), who reported UL without information on year of diagnosis (N = 94) or method of confirmation (N = 182), who did not complete a follow-up questionnaire (N = 1,610), or who had missing data on key covariates (N = 586) were also excluded. Finally, the 34 incident UL cases who reported a diagnosis of PCOS in the same year as their diagnosis of UL were excluded from the analysis because we could not determine which diagnosis occurred first. The remaining 23,571 women were followed for incidence of UL in the subsequent 6-year period. The small proportion of women who did not complete a follow-up questionnaire or who had incomplete data on covariates had a lower educational attainment than respondents, but were similar with respect to age, parity, age at menarche, and other established risk factors for UL.

Assessment of Exposure and Other Covariates

On the 1995 and 1997 questionnaires, women reported "polycystic ovary syndrome" or "Stein-Leventhal syndrome" under an open-ended question about "other serious illness" along with year of first diagnosis. On the 1999 and 2001 follow-up questionnaires, women were asked specifically whether they had been diagnosed with "poly-cystic ovarian syndrome" by a physician and, if so, to report the calendar year of first diagnosis. To ensure a prospective analysis, we required that the reported year of PCOS diagnosis precede that of the UL diagnosis. The date of diagnosis for PCOS does not necessarily refer to the actual onset of PCOS, which typically occurs around the time of adolescence (1,2).

On the baseline survey, data were obtained on age at menarche, oral contraceptive (OC) use, number of live births and stillbirths (parity), age at each birth, height, current weight, weight at age 18 years, physician-diagnosed diabetes, alcohol intake, cigarette smoking, education, and occupation. We also asked about history of infertility (defined as "trying to become pregnant for at least 1 year without success"), the age at which infertility first occurred, and its investigated causes. On the 2003 questionnaire, we asked about household income and number of individuals supported by this income. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). A validation study of anthropometric measures among 115 BWHS participants from the Washington, D.C. area showed high correlation (r = 0.97) between self-reported and technician-measured weight (25). Covariates that changed over time were updated on follow-up questionnaires (e.g., age, parity, and BMI), and were treated as time-dependent variables in the analysis.

An open-ended question about "medications used at least 3 days a week" was included on the baseline (1995) and follow-up questionnaires. We considered women with PCOS to be taking appropriate medications if they reported use of combined OCs or any of the following: biguanides (e.g., metformin), thiazolidinediones (e.g., pioglitazone), antiandrogens (e.g., cyproterone acetate, spironolactone, or flutamide), antiestrogens (e.g., clomiphene citrate), glucocorticoids (e.g., prednisone), ornithine decarboxylase inhibitors (e.g., eflornithine hydrochloride), and 5-α-reducatase inhibitors (e.g., finasteride) (26).

Assessment of Outcome

On the 1999, 2001, and 2003 follow-up questionnaires, women were asked about whether they had been diagnosed with "fibroids" in the previous 2-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic examination" and/or by "ultrasound and hysterectomy." In 2003, we changed "hysterectomy" to "surgery" because myomectomy was becoming more common as a treatment option, and divided "ultrasound" and "surgery" into two separate questions. Among cases reporting confirmation by "ultrasound and hysterectomy" or "surgery," a diagnosis was considered "hysterectomy-

confirmed" if the woman reported hysterectomy on the same questionnaire, and "ultrasound-confirmed" otherwise.

Ultrasound has been the standard method to confirm UL diagnoses in clinical practice (24). Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence (27,28). Because histologically confirmed cases represent only 10%–30% of cases for which ultrasound evidence is available, and because studies restricted to histologically confirmed cases may spuriously identify risk factors associated with disease severity or treatment preference (29), our outcome definition included cases confirmed by ultrasound or hysterectomy. Cases reporting confirmation by pelvic examination only were not considered as part of the case group, because such diagnoses may represent other pathologies (30).

We assessed the accuracy of self-report in a random sample of 248 cases. These cases were mailed supplemental surveys regarding their initial date of diagnosis, method of confirmation, symptoms, and treatment, and they were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission, and verified the self-report by medical record in 122 cases (96%). Among the 188 (76%) cases who completed the supplemental survey, 71% reported UL-related symptoms prior to being diagnosed with the condition. The most commonly reported symptoms were menorrhagia (53%) and pelvic pain (46%). When asked how their diagnosis had come to clinical attention, 55% of cases reported being diagnosed while seeking care for UL-related symptoms, and an additional 32% reported having UL clinically detected at the time of pelvic examination. The remaining 13% reported having UL detected incidentally while receiving care for another condition (> 85% cited "pregnancy" as the other condition).

There were no statistically significant differences between cases who did and did not release their medical records with respect to [1] established risk factors for UL; [2] self-reported method of confirmation; [3] the report of symptoms prior to the initial diagnosis; [4] the type of presenting symptoms; or [5] how the initial diagnosis was made (31). Therefore, the cases who released their medical records were likely to be representative of the larger case group.

Data Analysis

Incident cases were defined as women who self-reported a first diagnosis of UL, which was confirmed by ultrasound or hysterectomy. Cases confirmed by pelvic examination only were analyzed as part of the noncase group. Person-years at risk were calculated from the start of follow-up (March 1997) until the diagnosis of UL, menopause, death, loss to follow-up, or the end of follow-up (March 2003), whichever came first. Cox regression models, stratified by age (1-year intervals) and time period (1997–1999, 1999–2001, and 2001–2003), were used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for UL, and these models compared women with and without self-reported PCOS. A 95% CI that excluded 1.0 was considered statistically significant (i.e., $P < .05$). All analyses were carried out with the use of SAS statistical software (SAS, Inc., Cary, NC) (32).

A covariate was included in the multivariable analyses if the literature supported its role as an independent risk factor for UL, or if adding it to a model containing all other covariates changed the exposure IRR by ≥10% (33). Based on these criteria, we constructed three sets of multivariable models: [1] a model that controlled for age and time period; [2] a model that additionally controlled for reproductive and hormonal risk factors for UL, including age at menarche (years), parity (0, 1, 2, 3, or ≥4 births), infertility, age at first birth (years), years since last birth (< 5, 5–9, 10–14, or ≥15), and use of OCs (current, former, or never); and [3] a model that additionally controlled for lifestyle and socioeconomic risk factors for UL that may be related to PCOS, including BMI (< 20, 20–24, 25–29, 30–34, or ≥35), physician-

diagnosed diabetes (no, yes without medication, or yes with medication), cigarette smoking (current, former, or never), current alcohol consumption (< 1, 1–6, or ≥7 drinks per week), education (≤12, 13–15, 16, or ≥17 years), income (≤$25,000, $25,001–$50,000, $50,001–$100,000, > $100,000, or missing income), marital status (married or living with partner; divorced, separated, or widowed; or single), occupation (white collar, nonwhite collar, not employed or other employment, or missing occupation), and geographic region (Northeast, South, Midwest, and West). Results were stratified by "recency of Papanicolaou (Pap) smear," which we used as a proxy for gynecologic surveillance among participants.

Age was the strongest confounder of the PCOS and UL association, increasing the PCOS effect estimate by 13% when included in the Cox model. When we assessed the individual contribution of each covariate to the age-adjusted model, those with the largest influence on the PCOS effect estimate were parity and years since last birth (change in IRR estimate, 6% and 7%, respectively).

To examine whether the association between PCOS and UL was modified by education or other factors by which BWHS participants might differ from the general population of U.S. black women, we conducted likelihood ratio tests that compared models with and without cross-product terms between PCOS and the covariates. We assessed effect-measure modification by BMI because there is evidence that LH levels are higher in lean than in obese PCOS patients (34), and that hyperinsulinemia is more prominent in obese patients with PCOS (35). We also assessed effect modification by age, because there is evidence that women with PCOS have lower androgen levels and gain regular menstrual cycles when aging (36,37). Departures from the proportional hazards assumption were tested by a likelihood ratio test that compared models with and without cross-product terms between PCOS, time period, and age (< 32 versus ≥32). A cutoff of 32 years was used for age, because it provided an even number of person-years among women with PCOS in each age group, yielding optimal power to test for interaction.

RESULTS

Baseline characteristics of the sample according to self-reported physician-diagnosed PCOS are shown in Table 1. The prevalence of PCOS at the end of follow-up was approximately 1.2% (N = 275). The median age at first PCOS diagnosis was 28 years, and ranged from 13–51 years (data not shown). Among exposed cases, the mean difference in years between the diagnosis of PCOS and UL was 10 years (range, 1–17 years), with only 5 cases of UL occurring within 2 years of the PCOS diagnosis. The proportion of women with PCOS who reported taking medically appropriate drugs was 89%. Of those using medications, 85% were taking OCs (data not shown).

Women with PCOS were less likely to consume alcohol, but were more likely to be young, nulliparous, overweight or obese, or diabetic, and to report a history of infertility (particularly ovulatory infertility) at an early age. Nearly half (48%) of the women with PCOS were obese (BMI ≥30), compared to 35% of women without PCOS (data not shown). Women with and without PCOS had high levels of gynecologic surveillance (> 95%), as indicated by the report of a Pap smear in the previous 2 years. They were also similar with respect to various indicators of socioeconomic position, including education (Table 1), marital status, occupation, and income (data not shown).

During 114,373 person-years of follow-up, 3,631 incident cases of UL, confirmed by ultrasound (N = 2,926) or hysterectomy (N = 705), were reported (Table 2). The incidence of UL was 65% higher among women with PCOS than women without PCOS (fully adjusted

IRR, 1.65; 95% CI, 1.21–2.24). The IRRs remained elevated with increasing time after diagnosis of PCOS (test for trend, *P*=.80), even among women ≥6 years after diagnosis. When we confined the exposed group to women who were taking appropriate medications for PCOS, the IRR was 1.51 (95% CI, 1.08–2.12). Results were similar when analyses were restricted to women reporting a recent PAP smear, a proxy for a pelvic examination. Among this subgroup, the IRR comparing women with and without PCOS was 1.64 (95% CI, 1.20–2.24). Results were also similar when we included as part of the case group 697 women who reported UL confirmed by pelvic examination only (IRR, 1.57; 95% CI, 1.16–2.12).

Because there is evidence that disease characteristics for PCOS differ for lean and obese women, we stratified our analyses by BMI. The association between PCOS and UL was stronger among lean women than obese women (Table 3), but there was no statistical evidence of heterogeneity across BMI categories (test for interaction, *P*= .28).

The association between PCOS and UL appeared to vary with age (data not shown), such that the association was stronger among women who were 32 years of age or older (IRR, 1.89; 95% CI, 1.31–2.72) compared with women < 32 years of age (IRR, 1.22; 95% CI, 0.69–2.18). However, the IRRs were not statistically different from each other (test for interaction, *P*= . 24). The association between PCOS and UL was relatively uniform across levels of educational attainment (data not shown). The IRRs among women with ≤12, 13–15, and ≥16 years of education were 1.80 (95% CI, 0.65–5.00), 1.71 (95% CI, 1.00–2.91), and 1.62 (95% CI, 1.07–2.43), respectively (test for interaction, *P*= .88).

Associations were similar among women with (IRR, 1.72; 95% CI, 0.83–3.55) and without (IRR, 1.68; 95% CI, 1.19–2.36) a history of infertility, a condition that is positively associated with both PCOS and UL. Because insulin resistance and hyperinsulinemia are mechanisms by which PCOS may increase the risk of UL, we evaluated the association of physician-diagnosed diabetes with UL. Diabetes was inversely associated with risk of UL. Compared with women who never reported diabetes, fully adjusted IRRs for women reporting diabetes with and without use of medication were 0.77 (95% CI, 0.60–0.98) and 0.91 (95% CI, 0.64–1.28), respectively. Adjustment for diabetes in the main multivariable models made little difference in the effect estimate for PCOS.

DISCUSSION

In the present study of African-American women, PCOS was associated with a 65% increase in the risk of UL. There was no evidence that time after diagnosis of PCOS influenced the risk of UL, suggesting that the association was not accounted for by detection of UL shortly after a diagnosis of PCOS. The association between PCOS and UL was stronger among leaner women than obese women, and among older women than younger women, but these differences were not statistically significant.

Women with PCOS have several interrelated characteristics that may predispose them to UL, including insulin resistance, increased serum IGF-I levels (38), hyperandrogenism, and altered gonadotropin dynamics (e.g., elevated LH levels) (2). If chronic hyperinsulinemia and insulin resistance increase the risk of UL (15–17,19,20), one would expect to find an association of diabetes with UL. We found no such association; nor did we find any evidence that diabetes modifies the association between PCOS and UL. In addition, infertility, which may be influenced by PCOS (particularly ovulatory infertility), was not associated with UL in the BWHS (39). The association between PCOS and UL was evident after adjustment for infertility in multivariable models, and within subgroups of infertility, suggesting that infertility did not confound or modify the observed relation.

Prolonged anovulation represents one possible mechanism by which PCOS may influence the risk of UL, because it is often accompanied by continued secretion of E unopposed by P. Such an endogenous hormonal milieu may enhance the development and growth of UL, and others have postulated this to be the mechanism by which PCOS influences risk of endometrial cancer (2,40), which is also a hormone-dependent disease of the uterus.

Another plausible mechanism by which PCOS increases the risk of UL relates to hypersecretion of LH. Absolute levels of circulating LH and their ratio to FSH levels are significantly elevated in women with PCOS compared with controls (34,41). Elevated LH concentrations (> 95th percentile of normal) are observed in ~60% of women with PCOS (42,43), and the LH:FSH ratio may be elevated in up to 95% of nonovulating women with PCOS (34). LH may have a direct effect on the uterus, independent of its influence on the ovary (11,13,14). In addition, there is now evidence in humans that high levels of LH are associated with an increased risk of UL (12), and that suppression of LH and FSH with GnRH agonists can result in a reduction in volume of UL and significant uterine shrinkage (44,45). Our observation that the effect of PCOS is stronger among lean women than obese women lends support to the LH hypothesis, as levels of LH are highest among lean women with PCOS (34).

A limitation of our study is that PCOS was self-reported. Moreover, the definition of the disease itself continues to be debated among endocrinologists. The diagnosis of PCOS may depend on the astuteness of the physician and the awareness of the patient herself. The lower prevalence of self-reported PCOS in our cohort (1.7%) compared with a population-based sample of reproductive-aged black women (3.4%), who were screened using a widely accepted NIH definition of PCOS (3), suggests that some underreporting may have occurred (5). Because UL had not yet been diagnosed at the time of a woman's PCOS diagnosis, underreporting of PCOS in the present study would most likely have been random, and would have resulted in bias toward the null.

Women with PCOS typically seek medical care because of menstrual dysfunction, hirsutism, and/or infertility. If women with PCOS are more likely to undergo regular gynecologic screening relative to women without PCOS, this could explain the increased incidence of UL among women with PCOS. We attempted to minimize detection bias by restricting our analyses to women who reported similar levels of gynecologic surveillance, using "recency of Pap smear" as a proxy for a pelvic examination. The results did not change appreciably. We also controlled for a variety of indicators of socioeconomic position that may serve as proxies for access to medical care, including education, income, and occupation, but the results were not materially affected. Finally, when we examined the number of years between PCOS and UL diagnoses, we found no dramatic increase in risk for UL soon after the PCOS diagnosis, as would be expected if increased surveillance completely explained the results. Therefore, it is unlikely that our findings are explained by increased incidental detection of UL among women with PCOS.

We validated the self-report of UL through a detailed supplementary questionnaire and review of medical records. We were able to verify the diagnosis in > 96% of the cases from whom we obtained medical records. There was little difference between those who did and did not release their medical records with respect to reported symptomatology, method of diagnosis, or important risk factors for UL.

Women in the BWHS were not systematically screened for UL. It is likely that data from the BWHS more accurately represent the number of women with symptomatic tumors, because most cases in the validation survey reported symptoms prior to the initial diagnosis of the disease, and because a low percentage of cases (13%) was detected incidentally. Moreover,

rates of UL diagnoses in the BWHS are similar to rates reported in other U.S. studies based on prospective cohort and hospital discharge data (31).

Although the BWHS is a convenience sample of women with a higher level of education than the general population, prevalence estimates of suspected risk factors for UL, i.e., age at menarche (46), parity (46), and body weight (47), are similar to those found in nationally representative studies. As the association between PCOS and UL did not vary by education, the present findings might extend to the general population of U.S. black women.

Approximately 3,000,000 reproductive-aged women in the United States have PCOS (5,6), and its association with the development of several chronic diseases, such as diabetes, cardiovascular disease, and endometrial cancer, has been well-documented (2). Before UL can be added to the list of possible health consequences of PCOS, the positive association observed in the present study will require confirmation by future studies.

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References

1. Guzick D. Polycystic ovary syndrome: symptomatology, pathophysiology, and epidemiology. Am J Obstet Gynecol 1998;179(Suppl):S89 –93. [PubMed: 9855614]
2. Guzick DS. Polycystic ovary syndrome. Obstet Gynecol 2004;103:181–93. [PubMed: 14704263]
3. Zawadzki, JK.; Dunaif, A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif, A.; Givens, JR.; Haseltine, FP.; Merriam, GR., editors. Polycystic ovary syndrome. Boston: Blackwell; 1992. p. 377.-84.
4. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7. [PubMed: 14688154]
5. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998;83:3078–82. [PubMed: 9745406]
6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–9. [PubMed: 15181052]
7. Rebuffe-Scrive M, Cullberg G, Lundberg PA, Lindstedt G, Bjorntorp P. Anthropometric variables and metabolism in polycystic ovarian disease. Horm Metab Res 1989;21:391–7. [PubMed: 2777199]
8. Dahlgren E, Friberg LG, Johansson S, Lindstrom B, Oden A, Samsioe G, et al. Endometrial carcinoma; ovarian dysfunction—a risk factor in young women. Eur J Obstet Gynecol Reprod Biol 1991;41:143–50. [PubMed: 1936493]
9. Dahlgren E, Janson PO. Polycystic ovary syndrome: long-term effects. Ann Med 1993;25:307–8. [PubMed: 8217093]
10. Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992;71:599–604. [PubMed: 1336918]
11. Shemesh M. Actions of gonadotrophins on the uterus. Reproduction 2001;121:835–42. [PubMed: 11373169]
12. Baird DD, Kesner JS, Dunson DB. Luteinizing hormone in premenopausal women may stimulate uterine leiomyomata development. J Soc Gynecol Invest 2006;13:130–5.
13. Tesarik J, Hazout A, Mendoza C. Luteinizing hormone affects uterine receptivity independently of ovarian function. Reprod Biomed Online 2003;7:59–64. [PubMed: 12930575]

14. Stewart EA. Gonadotropins and the uterus: is there a gonad-independent pathway? J Soc Gynecol Invest 2001;8:319.
15. Burroughs KD, Howe SR, Okubo Y, Fuchs-Young R, LeRoith D, Walker CL. Dysregulation of IGF-I signaling in uterine leiomyoma. J Endocrinol 2002;172:83–93. [PubMed: 11786376]
16. Giudice LC, Irwin JC, Dsupin BA, Pannier EM, Jin IH, Vu TH, et al. Insulin-like growth factor (IGF), IGF binding protein (IGFBP), and IGF receptor gene expression and IGFBP synthesis in human uterine leiomyomata. Hum Reprod 1993;8:1796–806. [PubMed: 7507128]
17. Wolanska M, Bankowski E. An accumulation of insulin-like growth factor I (IGF-I) in human myometrium and uterine leiomyomas in various stages of tumour growth. Eur Cytokine Netw 2004;15:359–63. [PubMed: 15627646]
18. Gloudemans T, Prinsen I, Van Unnik JA, Lips CJ, Den Otter W, Sussenbach JS. Insulin-like growth factor gene expression in human smooth muscle tumors. Cancer Res 1990;50:6689–95. [PubMed: 2208134]
19. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev 1987;8:132–41. [PubMed: 3301317]
20. Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. Am J Epidemiol 2001;153:11–9. [PubMed: 11159140]
21. Boynton-Jarrett R, Rich-Edwards J, Malspeis S, Missmer SA, Wright R. A prospective study of hypertension and risk of uterine leiomyomata. Am J Epidemiol 2005;161:628–38. [PubMed: 15781952]
22. Doi SAR, Al-Zaid M, Towers PA, Scott CJ, Al-Shoumer KAS. Irregular cycles and steroid hormones in polycystic ovary syndrome. Hum Reprod 2005;20:2402–8. [PubMed: 15932911]
23. Rosenberg L, Adams-Campbell LL, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. J Am Med Wom Assoc 1995;50:56–8. [PubMed: 7722208]
24. Stewart EA. Uterine fibroids. Lancet 2001;357:293–8. [PubMed: 11214143]
25. Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology 2005;16:346–54. [PubMed: 15824551]
26. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223–36. [PubMed: 15788499]
27. Loutradis D, Antsaklis A, Creatsas G, Hatzakis A, Kanakas N, Gougoulakis A, et al. The validity of gynecological ultrasonography. Gynecol Obstet Invest 1990;29:47–50. [PubMed: 2190879]
28. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol 2002;186:409–15. [PubMed: 11904599]
29. Schwartz, SM.; Marshall, LM. Uterine leiomyomata. In: Goldman, MB.; Hatch, MC., editors. Women and health. San Diego, CA: Academic Press; 2000. p. 240.-52.
30. Robboy, SJ.; Andersen, MC.; Russell, P. Pathology of the female reproductive tract. London: Churchill Livingstone; 2002.
31. Wise LA, Palmer JR, Stewart EA, Rosenberg L. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. Obstet Gynecol 2005;105:563–8. [PubMed: 15738025]
32. SAS Institute, Inc. SAS/STAT user's guide, version 802. Cary, NC: SAS Institute; 2002.
33. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340–9. [PubMed: 2916724]
34. Taylor AE, McCourt B, Martin KA, Anderson EJ, Adams JM, Schoenfeld D, et al. Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. J Clin Endocrinol Metab 1997;82:2248–56. [PubMed: 9215302]
35. Pasquali R, Casimirri F, Venturoli S, Antonio M, Morselli L, Reho S, et al. Body fat distribution has weight-independent effects on clinical, hormonal, and metabolic features of women with polycystic ovary syndrome. Metabolism 1994;43:706–13. [PubMed: 8201958]

36. Elting MW, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. Hum Reprod 2000;15:24–8. [PubMed: 10611183]

37. Bili H, Laven J, Imani B, Eijkemans MJ, Fauser BC. Age-related differences in features associated with polycystic ovary syndrome in normogonadotrophic oligoamenorrhoeic infertile women of reproductive years. Eur J Endocrinol 2001;145:749–55. [PubMed: 11720900]

38. Berker B, Emral R, Demirel C, Corapcioglu D, Unlu C, Kose K. Increased insulin-like growth factor-I levels in women with polycystic ovary syndrome, and beneficial effects of metformin therapy. Gynecol Endocrinol 2004;19:125–33. [PubMed: 15697073]

39. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, et al. Reproductive factors, hormonal contraception and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 2004;159:113–23. [PubMed: 14718211]

40. Gadducci A, Gargini A, Palla E, Fanucchi A, Genazzani AR. Polycystic ovary syndrome and gynecological cancers: is there a link? Gynecol Endocrinol 2005;20:200–8. [PubMed: 16019362]

41. Fauser BC, Pache TD, Lamberts SW, Hop WC, de Jong FH, Dahl KD. Serum bioactive and immunoreactive luteinizing hormone and follicle-stimulating hormone levels in women with cycle abnormalities, with or without polycystic ovarian disease. J Clin Endocrinol Metab 1991;73:811–7. [PubMed: 1909705]

42. van Santbrink EJ, Hop WC, Fauser BC. Classification of normogonadotropic infertility: polycystic ovaries diagnosed by ultrasound versus endocrine characteristics of polycystic ovary syndrome. Fertil Steril 1997;67:452–8. [PubMed: 9091329]

43. Laven JS, Imani B, Eijkemans MJ, Fauser BC. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynecol Surv 2002;57:755–67. [PubMed: 12447098]

44. Nakamura Y, Yoshimura Y, Yamada H, Ubukata Y, Ando M, Suzuki M. Treatment of uterine leiomyomata with a luteinizing hormone-releasing hormone agonist: the possibility of nonsurgical management in selected perimenopausal women. Fertil Steril 1991;55:900–5. [PubMed: 1902420]

45. Stewart EA, Friedman AJ. Steroidal treatment of myomas: preoperative and long-term medical therapy. Semin Reprod Endocrinol 1992;10:344–57.

46. Abma JC, Chandra A, Mosher WD, Peterson LS, Piccinino LJ. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth [Series 23, No. 9]. Vital Health Stat 1997;23:19.

47. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. J Am Med Assoc 2002;288:1723–7.

TABLE 1

Characteristics of 23,571 premenopausal women according to self-reported diagnosis of polycystic ovary syndrome: the Black Women's Health Study, 1997.

Characteristic	Polycystic ovary syndrome	
	Yes (N = 275)	No (N = 23,296)
Mean		
Age (y)	30.3	34.9
Education as of 1995 (y)	15.0	14.9
Body mass index (kg/m^2)	30.6	27.9
Body mass index at age 18 years (kg/m^2)	22.4	21.8
Age at menarche (y)	12.2	12.3
Percentage		
Parous	39.6	56.8
History of infertility (1995)	24.4	10.3
Ovulatory infertility	7.7	1.0
Other type of infertility	18.1	9.3
Age at first experience of infertility (1995)		
< 25	9.8	4.0
25–29	9.3	3.3
≥30	3.6	2.5
History of diabetes	7.1	3.9
Papanicolaou smear in previous 2 years	98.3	95.4
Oral contraceptive use		
Current	22.6	19.5
Former	60.5	62.9
Current cigarette smoker	12.5	13.3
Current alcohol intake (≥1 drinks/week)	16.6	30.0

Note: Number with PCOS includes all women who reported their condition over the follow-up period. Characteristics are derived from 1997 questionnaire (start of follow-up), unless otherwise noted. Means and percentages are adjusted for age in 1997 in 5-year intervals. Infertility categories are not mutually exclusive. "Other type of infertility" includes: tubal blockage, endometriosis, spouse, cervical mucus factors, not investigated, not found, and other.

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TABLE 2

Polycystic ovary syndrome and risk of uterine leiomyomata in the Black Women's Health Study, 1997–2003.

	Cases confirmed by ultrasound or hysterectomy					
	Cases	**Person- years**	**Crude IR**	**Model 1, IRR (95%CI)**	**Model 2, IRR (95%CI)**	**Model 3, IRR (95%CI)**
Overall	3,631	114,373	31.7			
PCOS						
No	3,589	113,528	31.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	42	845	49.7	1.82 (1.34–2.47)	1.64 (1.21–2.23)	1.65 (1.21–2.24)
Years after PCOS diagnosis						
< 2	5	101	49.4	1.83 (0.76–4.41)	1.66 (0.69–4.01)	1.67 (0.70–4.03)
2–3	9	261	34.5	1.32 (0.69–2.55)	1.20 (0.62–2.31)	1.19 (0.62–2.29)
4–5	13	200	65.0	2.47 (1.43–4.27)	2.18 (1.26–3.76)	2.20 (1.27–3.80)
≥6	15	283	52.9	1.81 (1.093.00)	1.65 (0.99–2.75)	1.66 (1.00–2.76)
Test for ordinal trend						*P*= .80

Note: IR = incidence rate per 1,000 person-years, IRR = incidence rate ratio, and CI = confidence interval. Model 1 is adjusted for age and time period. Model 2 is additionally adjusted for age at menarche, parity, age at first birth, years since last birth, OC use, and infertility. Model 3 is additionally adjusted for BMI, diabetes, current alcohol consumption, smoking, education, marital status, occupation, income, and geographic region.

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TABLE 3

Polycystic ovary syndrome and risk of uterine leiomyomata, according to BMI: the Black Women's Health Study, 1997–2003.

	Cases confirmed by ultrasound or hysterectomy					
	Cases	**Person- years**	**Crude IR**	**Model 1, IRR (95% CI)[a]**	**Model 2, IRR (95% CI)[b]**	**Model 3, IRR (95% CI)[c]**
BMI < 25 (kg/m^2)						
PCOS						
1,302	42,424	30.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	
No						
10	197	50.7	1.99 (1.07–3.72)	1.95 (1.04–3.65)	1.97 (1.05–3.69)	
Yes						
BMI 25–29 (kg/m^2)						
PCOS						
1,098	33,809	32.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	
No						
17	253	67.1	2.30 (1.41–3.73)	2.04 (1.26–3.32)	2.07 (1.27–3.37)	
Yes						
BMI ≥30 (kg/m^2)						
PCOS						
1,189	37,295	31.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	
No						
15	395	38.0	1.38 (0.83–2.31)	1.29 (0.77–2.15)	1.29 (0.77–2.16)	
Yes						

Note: IR = incidence rate per 1,000 person-years, IRR = incidence rate ratio, CI = confidence interval. Model 1 is adjusted for age and time period. Model 2 is additionally adjusted for age at menarche, parity, age at first birth, years since last birth, OC use, and infertility. Model 3 is additionally adjusted for BMI (continuous variable), diabetes, current alcohol consumption, smoking, education, marital status, occupation, income, and geographic region.

Wise. PCOS and risk of uterine leiomyomata. Fertil Steril 2007.