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Lower prevalence of non-cavity-distorting uterine fibroids in patients with PCOS than those with unexplained infertility

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Abstract

Objective: To study whether there is a difference in the prevalence of non-cavity-distorting uterine fibroids between infertile patients with polycystic ovary syndrome (PCOS) and those with unexplained infertility (UI).

Design: A secondary analysis of data from three randomized clinical trials.

Setting: Academic health centers.

Patients: A total of 2249 patients with a normal uterine cavity.

Interventions(s): None

Main Outcome Measure(s): The presence or absence of non-cavity-distorting fibroids.

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Supplemental figure 1. Receiver operating characteristic (ROC) curves and areas under the curve (AUC) of the final model for the presence of women with non-cavity-distorting fibroids. P=0.87 for the Hosmer and Lemeshow (HL) goodness-of-fit test.

Results: Compared to women with UI, those with PCOS were younger, had a higher body mass index, were more likely to be Hispanic and African American, with a lower percentage of prior conception and live birth, a higher percentage of current smokers and lower percentage of current alcohol users, had a higher total testosterone, fasting insulin, and homeostatic model assessment-insulin resistance. The prevalence of women with non-cavity-distorting uterine fibroids was lower in women with PCOS than those with UI (6.7% vs 12.4%, p<0.001); this result held after patients were divided into Black and non-Black, or three different body mass index groups. After adjustment for all the other variables in the final model, patients with PCOS had a significantly lower prevalence of fibroids than those with UI (Odds Ratio=0.54, 95% confidence interval, 0.36–0.79, p=0.002). No difference in the prevalence of non-cavity-distorting fibroids with any dimensions >=4 cm nor the volume of the largest fibroid was found between the two groups.

Conclusion(s): A lower prevalence of non-cavity-distorting uterine fibroids was found in infertile women with PCOS than those with UI.

Capsule

The prevalence of non-cavity-distorting fibroids was compared between two infertile patient groups; it was lower in patients with polycystic ovary syndrome than those with unexplained infertility.

Keywords

PCOS; unexplained infertility; non-cavity-distorting fibroids; risk factor

Introduction

Uterine leiomyomata (fibroids) are benign monoclonal tumors that develop from the myometrium of the uterus. They are the most common tumors of the female reproductive tract, clinically apparent in 20% to 40% of women in their reproductive years (1, 2). Fibroids are heterogeneous in pathophysiology, size, location, and clinical symptomatology (3, 4). Intramural and/or subserosal fibroids that do not distort the uterine cavity can be asymptomatic or symptomatic (4); their effect on pregnancy outcomes remains poorly understood with conflicting results. Some studies showed that no difference existed in pregnancy outcome between patients with and without non-cavity-distorting fibroids (5–7). In contrast, many studies reported that uterine fibroids that do not distort the uterine cavity were associated with a decreased implantation rate and pregnancy rate (8–10), especially for the intramural fibroids with a size >4 cm (11, 12).

Many factors have been associated with the occurrence of fibroids (regardless of cavity-or non-cavity-distorting fibroids), including advancing reproductive age, Black race, obesity, and nulliparity (13, 14). Recent studies showed that some hormonal and metabolic factors are also associated with the development of fibroids (4). While increasing luteinizing hormone (LH) levels were associated with increased fibroid development (15); hyperinsulinemia and diabetes were inversely associated with the prevalence fibroids (16–18) in some studies. However, other investigators have hypothesized that insulin stimulates fibroid growth (19, 20). Hypertension, which often accompanies hyperinsulinemia in

conditions such as the metabolic syndrome, has been associated with an increased risk of fibroids (21, 22). All of these attributes: hyperinsulinemia, insulin resistance, increased LH, and hypertension are common in patients with polycystic ovary syndrome (PCOS) (23, 24), which affects 5 to 10% of reproductive age women and is the most common cause of anovulatory infertility. Whether PCOS is associated with an increased or decreased risk of fibroids has received scant attention in the medical literature, with one study indicating a 65% increased risk of fibroids among Black women with PCOS when compared to those without PCOS (18) and another study showing a decreased risk for fibroids for patients with PCOS when compared to those with normal ovaries (25).

The National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network Pregnancy in Polycystic Ovary Syndrome I (PPCOS I) (26), Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) (27), and Assessing Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) (28) studies provide a unique opportunity to investigate whether an association exists in women with PCOS and non-cavity-distorting fibroids. All patients enrolled in PPCOS I and PPCOS II were infertile oligoovulatory women with PCOS; women enrolled in AMIGOS were diagnosed with unexplained infertility (UI), and served as a control group. As an inclusion criterion, these three studies required every patient to have a normal uterine cavity at the time of enrollment. However, a small number of patients underwent uterine surgeries to remove fibroids before enrollment, and subsequently they met this inclusion criterion by the time of enrollment. To account for the possibility that this subgroup of patients might be different from the remaining patients, the current analysis excluded all females with any history prior to enrollment of fibroids which distorted the uterine cavity. Here, we focus on the comparison of the prevalence of uterine intramural and/or subserosal (non-cavity distorting) fibroids between infertile patients with PCOS and those with UI. Since a much higher prevalence and greater severity of fibroids have been consistently observed in African American women (13, 29), and PCOS characteristics differ in lean and obese women (30, 31), we stratified our analysis by race and various body mass index (BMI) groups. In addition, since the size of the fibroid may play a role in its effect on infertility (11, 12), we compared the prevalence of the non-cavity-distorting fibroids with any dimension >=4 cm and the total volume of the largest fibroid between the two groups.

Materials and Methods

Design and study population

This is a secondary analysis utilizing data from the PPCOS I (http://clinicaltrials.gov: NCT00068861), PPCOS II (NCT00719186), and AMIGOS (NCT01044862) trials. PPCOS I was a multicenter, double-blind, randomized clinical trial, comparing live-birth rate in response to treatment with clomiphene citrate plus placebo, metformin plus placebo, or combination clomiphene citrate plus metformin for up to a total of five cycles (32). In brief, 626 oligoovulatory infertile women, aged 18–39 years, with PCOS diagnosed by Rotterdam criteria (24) were enrolled. Participants with other causes of infertility were excluded. Documentation of a normal uterine cavity and at least one patent fallopian tube were required prior to enrollment, as well as a semen analysis with at least 20 million sperm per

milliliter for the male partners. All participants were in good health with no major medical disorders. PPCOS II was a multicenter, double-blind, randomized clinical trial comparing live-birth rate in response to treatment with clomiphene citrate or letrozole for up to a total of five cycles (33). In brief, 750 women with PCOS were enrolled. Females were between 18 and 40 years, with anovulation, combined with either hyperandrogenism or polycystic appearing ovaries by ultrasound. Documentation of tubal patency and a normal uterine cavity was required prior to enrollment, as well as a semen analysis with at least 14 million sperm per milliliter for the male partners. Key exclusion criteria included history of major medical diseases, including diabetes and cavity distorting uterine fibroids. AMIGOS was a prospective, multicenter randomized clinical trial that evaluated the outcomes of live birth and multiple gestations associated with ovarian stimulation and intrauterine insemination in couples with UI (34). In brief, 900 couples were enrolled. Participating women were between 18 and 40 years with regular ovulatory menses, had a normal uterine cavity with at least one patent fallopian tube, and had a male partner with a semen specimen with at least 5 million motile sperm in the ejaculate. Key exclusion criteria were history of major medical diseases, including diabetes, endometriosis, PCOS, and cavity distorting uterine fibroids.

Ethical approval

For all 3 studies, Institutional Review Board approval was obtained at each study site, and all participants gave written informed consents. The investigation was monitored by an independent Data and Safety Monitoring Board.

Data collection

Demographic characteristics, medical history, and lifestyle profiles were obtained using standardized forms. Patients also underwent Ferriman-Gallwey hirsutism scoring measurements. Fasting blood collected at baseline or screening was used for all hormonal assays. Samples were batched and analyzed at the Ligand Assay and Analysis Core Laboratory at the University of Virginia. All had acceptable quality control measures by Partnership for the Accurate Testing of Hormones standards (35). We have previously published the quality control standards of these assays and all had inter- and intra-assay coefficients of variation < 10% (27, 28). Presence or absence of fibroids, and three dimensions of the largest fibroid (PPCOS II and AMIGOS patients only) were recorded during transvaginal ultrasound (using a 5–9 mHz vaginal probe, most centers used 5 mHz) (27, 28). Per the original protocols, the location, total number and aggregate volume of all fibroids were not recorded.

Data analyses

Analysis was conducted using the combined patients from PPCOS I (n=626), PPCOS II (n=750), and AMIGOS (n=900) studies. Of these 2276 patients, 27 were excluded from analysis because they had a history of surgery to remove fibroids (1 from PPCOS I study, 4 from PPCOS II study, and 22 from AMIGOS study). The main outcome of interest is the presence of non-cavity-distorting fibroids (fibroids with a normal uterine cavity), identified by transvaginal ultrasound performed at either the screening or baseline visit (before taking any study medication). Other outcomes include the presence of any fibroid with a dimension >=4 cm and the volume (cm^3, length x width x height) of the largest fibroid. Baseline patient

demographic characteristics, medical history, lifestyle factors, and circulating hormonal levels were selected as covariates.

Continuous variables were expressed as median (interquartile range, IQR), with a Wilcoxon rank-sum test (also called the Mann–Whitney U test) used for testing differences between patients with PCOS and those with UI. Categorical data were reported as frequencies and percentages; differences in these measures between the two groups were assessed by a chi-square analysis, with Fisher's exact test used for expected frequencies of less than 5. Logistic regression was used to establish a final model for the presence of fibroids. All variables were introduced into a multivariable logistic regression analysis in a stepwise fashion, using a *P* value of <.10 to enter and a *P* value of <.05 to remain. To assess the predictive/discriminative power of final models, we constructed receiver operating characteristic (ROC) curves and calculated the areas under the curve (AUC). A model with perfect discrimination has an AUC of 1.0, while a model with no discrimination has an AUC of 0.5. We also performed the Hosmer-Lemeshow (HL) test for goodness-of-fit of the final logistic regression models, with a *P* value of >.05 indicating a good fit of the data. In addition, for each covariate selected from the stepwise procedure, the interaction effects between the patient group and selected covariates were then assessed, and those interactions that were significant at the 0.05 level were then included in the final model. Analyses were performed with SAS software, version 9.4 (SAS Institute). Statistical significance was defined as a two-sided P value of less than 0.05.

Results

Baseline characteristics for infertile patients with PCOS or UI.

We compared demographic characteristics for PCOS and UI patients (Table 1). Patients with PCOS had a lower age (P<0.001), higher BMI (P<0.001), higher waist circumference (P<0.001), higher waist/hip ratio (P<0.001), and higher hirsutism score (P<0.001) when compared to those with UI. Patients with PCOS were more likely to be Hispanic (P<0.001), Black (P<0.001), to have a lower percentage with a professional occupation (P<0.001) and a lower annual household income (P<0.001), when compared to those with UI.

Comparison of medical history and lifestyle factors between patients with PCOS and those with UI is shown in Table 2. Patients with PCOS had a lower percentage of a prior conception (P=0.002) and pregnancy loss (P<0.001), a higher percentage of having a prior diagnosis of infertility (P<0.001), a higher percentage of having a history of high blood pressure (P<0.001), a higher percentage of current smokers (P<0.001) and a lower percentage of current alcohol users (P<0.001).

Supplemental table 1 compares circulating hormones between patients with PCOS and those with UI. As expected, patients with PCOS had a higher value of total testosterone (P<0.001), free androgen index (P<0.001), fasting insulin (P<0.001), proinsulin (P<0.001), fasting glucose (P<0.001), and homeostatic model assessment-insulin resistance (HOMA-IR) than those with UI. Patients with PCOS also had lower sex hormone-binding globulin (SHBG) than those with UI (P<0.001).

Prevalence of non-cavity-distorting fibroids in patients with PCOS and UI

Table 3 shows the prevalence of women with non-cavity-distorting fibroids in patients with PCOS and those with UI. The prevalence of women with non-cavity-distorting fibroids was 6.7% (92 out of 1371) for patients with PCOS and 12.4% (109 out of 878) for patients with UI ($p<0.001$), with no difference existed between PPCOSI and PPCOSII patients [6.6% (41 out of 625) vs 6.8% (51 out of 746) respectively, $p=0.84$, data not shown]. In addition, for PPCOSII patients, no difference in the prevalence non-cavity-distorting fibroids was found between those with ovulatory dysfunction and hyperandrogenism (1990 NIH criteria PCOS) and those with ovulatory dysfunction with polycystic ovaries (non-hyperandrogenic PCOS) [6.9% (48/695, and 7.1% (3/42) respectively, $p=1.00$, data not shown]. When stratified by Black and non-Black race groups, the prevalence of women with non-cavity-distorting fibroids was significantly higher in patients with UI than those with PCOS in both race groups, with a prevalence of 10.7% versus 35.9% among Black women with PCOS and UI, respectively ($p<0.001$, Table 3) and 6.0% versus 10.1% in the non-Black women with PCOS and those with UI, respectively ($p=0.001$). Similarly, when stratified by 3 different BMI groups, the prevalence of women with non-cavity-distorting fibroids was significantly lower in patients with PCOS than those with UI in all of the groups, with a prevalence of 2.8% vs 10.6% ($p<0.001$), 5.7% vs 12.8% ($p=0.02$), and 7.8% vs 15.3% ($p<0.001$) for patients with PCOS vs those with UI in the BMI <25, BMI 25–29, and BMI >=30 groups, respectively (Table 3). No significant difference, in the prevalence of non-cavity-distorting fibroids with any dimension >=4 cm nor the volume of the largest fibroid, existed between patients with PCOS and those with UI for the overall patients or the sub-groups with different races and various BMIs (all the p values >0.20, Table 3).

Adjusted risk of PCOS on the prevalence of non-cavity-distorting fibroids

The independent risk factors for, and the adjusted risk of PCOS on the prevalence of non-cavity-distorting fibroids were obtained by using the multivariable analysis. All the variables that survived in the final model are shown in Table 4. After adjustment for age, waist circumference, ethnicity, race, HOMA-IR, prior therapy for infertility, and history of alcohol use, patients with PCOS showed a significantly lower prevalence of fibroids than those with UI (Odds Ratio=0.54, 95% confidence interval (CI), 0.36–0.79, $p=0.002$). The ROC curves, AUC, and the HL goodness fit test for the final models are shown in Supplemental figure 1. The AUC of 0.76 and a p value of 0.87 for the HL goodness fit test indicate that the model has a good discrimination between patients with non-cavity-distorting fibroids and those without, and that the model has a good calibration. The association between PCOS and non-cavity-distorting fibroids was stronger among Black women than non-Black women (Table 3), but there was no statistically significant evidence of heterogeneity across race groups (test for interaction=0.06). BMI did not remain in the final model; when forcing BMI and its interaction with patient group in the model, no evidence of heterogeneity across BMI groups was found ($p=0.26$ for the interaction).

Discussion

We found that infertile patients with PCOS had a lower prevalence of non-cavity-distorting fibroids at baseline than those with UI. The association was similar between Black and non-

Black women, and among women across different BMI categories. No difference existed for prevalence of non-cavity-distorting fibroid with any dimension >=4 cm nor the total volume of the largest fibroid between the two groups.

This is the first study showing that patients with PCOS have a lower prevalence of non-cavity-distorting fibroids than those with UI, consistent with one previous finding that patients with PCOS had a lower percentage of fibroids when compared to those with normal ovaries (25). It differs from another previous finding that PCOS was associated with a 65% increased risk of fibroids among Black women (18). When limiting our analysis to include only the Black women, a diagnosis of PCOS was still associated with a significantly lower prevalence of non-cavity-distorting fibroids with [Odds ratio=0.26, 95% CI, 0.12–0.58, $p<0.001$, data not shown) or without (Table 3) adjustment for other covariates. Thus, the difference in the two study findings is unlikely to be due to difference in race of study participants. It may be related to the fact that the previous study relied upon self-report to diagnose PCOS and did not systematically screen all patients for the presence of fibroids with the use of transvaginal ultrasound (18). Another possible explanation for the lack of agreement between our study and the previous report is that our study was limited to non-cavity-distorting fibroids, while the previous study considered submucosal as well as non-cavity-distorting fibroids. One advantage of our study is the systematic characterization and more accurate diagnosis of women with PCOS and the confirmation of the presence of fibroids by transvaginal ultrasound in all study participants prior to any treatment. In other words, the data analyzed herein were of higher quality.

It has been shown that the size of non-cavity-distorting fibroids plays important roles in their effect on infertility; those with a size >4 cm had a lower pregnancy (12) and delivery rate (11). Our finding showed that no difference existed in the prevalence of non-cavity-distorting fibroids with any dimension >=4 cm nor the volume of the largest fibroids between patients with PCOS and those with UI, suggesting that the underlying mechanisms for UI may only influence the occurrence but not the growth/development of the non-cavity-distorting fibroids, and thus may have limited impact on pregnancy outcome when compared to those with PCOS. Since the patients in the original studies were highly selected, it would also be possible that most of the patients with large fibroid size were excluded from the studies and thus a small number of patients with fibroids >=4 cm would have limited the power to detect any difference (Table 3). Since the information about the total number and the aggregate volume of all fibroids was not available, whether the overall fibroid burden was different between the two groups is unclear and warrants future investigation.

The reason for a lower prevalence of non-cavity distorting fibroids in the women with PCOS compared to those with UI is unknown. Patients with PCOS have anovulation, with resultant limited exposure of uterine myometrium to progesterone (36). Progesterone has been shown to stimulate the growth of leiomyoma through a set of key genes that regulate both apoptosis and proliferation (37, 38). Thus, the reduced exposure of women with PCOS to progesterone may explain our observed findings. Consistent with these observations we found that women with previous treatment for infertility, with probable increased ovulation rates and progestin exposure, had a significantly higher prevalence of fibroids than in those not having previous infertility treatment [Adjusted OR=1.53 (CI 1.10–2.13)] (Table 4). Additionally

hyperinsulinemia, insulin resistance, increased level of LH, diabetes, and hypertension (23, 24) are associated with PCOS. Previous findings that hyperinsulinemia and diabetes were inversely associated with fibroids (16–18) were consistent with our findings. However, our results contradict other previous reports. For example, other investigators reported that an increase in LH levels was associated with increased fibroid development (15) which we did not find (data not shown); hypertension was reportedly associated with an increased risk of fibroids (21, 22) but we did not observe this association. Our findings that higher waist circumference and HOMA-IR were associated with an increased risk of non-cavity-distorting fibroids (Table 4) suggests that hyperinsulinemia is not the reason for the decreased prevalence of non-cavity-distorting fibroids observed in patients with PCOS.

Although the prevalence and severity of fibroids were different between Black and non-Black women (13, 29), and PCOS characteristics may differ between lean and obese women (30, 31), our results that patients with PCOS was associated with a lower prevalence of non-cavity-distorting fibroids than those with UI was not significantly different between Black and non-Black women, nor among the women with different BMIs, suggests that no evidence of heterogeneity of the observed association existed across different race and BMI groups.

Our findings that older age and Black race were associated with higher prevalence of non-cavity-distorting fibroids (Table 4) are consistent with the work of others (4, 13, 16, 29, 39). In addition, we showed that previous or current use of alcohol was independently associated with a decreased prevalence of non-cavity-distorting fibroids, which differs from prior findings that alcohol use was associated with an increased prevalence of fibroids (40–42). The underlying mechanisms for this association are unknown.

The present study has several strengths and weaknesses. Among the strengths is the large sample size, and multicenter design of our three studies, which represent the largest US-based cohort of infertile couples studied to date. The complete characterization of the women with demographics, medical history, lab tests, and ultrasound findings are additional strengths. One weakness of our study is that women with abnormal uterine cavity were excluded from our original studies and that we excluded any patients who had a prior surgery to remove fibroids. How the exclusion of these patients affects the association that we have identified is unknown; however this exclusion was applied across all women with either PCOS or UI. Another weakness is the fact that the three included trials were not conducted at the same time period; PPCOSI was conducted much earlier than PPCOSII and AMIGOS trials. Also difference may exist in ultrasound equipment and the data interpretation among sonographers. However, a standard protocol was used for obtaining sonographic measurements for PPCOSII and AMIGOS studies; more than half of the subjects were recruited at the same sites for all three studies and 88% of subjects were recruited at the same sites for both PPCOSII and AMIGOS studies. The very similar prevalence of non-cavity-distorting fibroids between PPCOSI and PPCOSII patients suggests it is unlikely that the lower prevalence of fibroids in PCOS patients was due to the different time periods when the trials were conducted and the difference in ultrasound equipment and the data interpretation among sonographers. In addition, participants for all the original studies were all infertile patients. The results may be different for reproductive-

aged fertile women; thus firm conclusions about how representative our patients are to the general population should be made with caution.

In summary, this study showed that infertile oligoovulatory women with PCOS had a reduced prevalence of non-cavity-distorting fibroids compared to regularly ovulating women with unexplained infertility. This association was not different with regard to Black and non-Black race groups, nor the patients with different BMIs. With a high prevalence of both PCOS and fibroids in reproductive-age women, future studies are needed to further evaluate the association between PCOS, fibroids and infertility in a more general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest

HH, HK, FS, RA, NS, and EE have nothing to declare. MPD received grant support from funding from NICHD, Advanced Reproductive Care, AbbVie, ObsEva, and Bayer. RL is a consultant for Ogeda, Kindex, Fractyl, and Bayer and received funding from Ferring. CC received funding from NIH/NICHD. RR received funding from AbbVie. PC received funding from NIH. GMC received NIH funding, grants, personal fees and other from Abbvie Pharmaceuticals. KRH received Roche Diagnostics and Ferring International Pharmascience Center US funding. HZ received NIH Funding.

References

1. Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol 2004;104:393–406. [PubMed: 15292018]
2. Stewart EA. Uterine fibroids. Lancet 2001;357:293–8. [PubMed: 11214143]
3. Whynott RM, Vaught KCC, Segars JH. The Effect of Uterine Fibroids on Infertility: A Systematic Review. Semin Reprod Med 2017;35:523–32. [PubMed: 29100240]
4. Wise LA, Laughlin-Tommaso SK. Epidemiology of Uterine Fibroids: From Menarche to Menopause. Clin Obstet Gynecol 2016;59:2–24. [PubMed: 26744813]
5. Klatsky PC, Lane DE, Ryan IP, Fujimoto VY. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. Hum Reprod 2007;22:521–6. [PubMed: 16997932]
6. Styer AK, Jin S, Liu D, Wang B, Polotsky AJ, Christianson MS et al. Association of uterine fibroids and pregnancy outcomes after ovarian stimulation-intrauterine insemination for unexplained infertility. Fertil Steril 2017;107:756–62 e3. [PubMed: 28089575]

7. Surrey ES, Lietz AK, Schoolcraft WB. Impact of intramural leiomyomata in patients with a normal endometrial cavity on in vitro fertilization-embryo transfer cycle outcome. Fertil Steril 2001;75:405–10. [PubMed: 11172848]
8. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod 2010;25:418–29. [PubMed: 19910322]
9. Christopoulos G, Vlismas A, Salim R, Islam R, Trew G, Lavery S. Fibroids that do not distort the uterine cavity and IVF success rates: an observational study using extensive matching criteria. BJOG 2017;124:615–21. [PubMed: 27921379]
10. Zepiridis LI, Grimbizis GF, Tarlatzis BC. Infertility and uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2016;34:66–73. [PubMed: 26856931]
11. Yan L, Ding L, Li C, Wang Y, Tang R, Chen ZJ. Effect of fibroids not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril 2014;101:716–21. [PubMed: 24424367]
12. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. Fertil Steril 2004;81:582–7. [PubMed: 15037406]
13. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010;28:204–17. [PubMed: 20414843]
14. Parazzini F Risk factors for clinically diagnosed uterine fibroids in women around menopause. Maturitas 2006;55:174–9. [PubMed: 16533580]
15. Baird DD, Kesner JS, Dunson DB. Luteinizing hormone in premenopausal women may stimulate uterine leiomyomata development. J Soc Gynecol Investig 2006;13:130–5.
16. Templeman C, Marshall SF, Clarke CA, Henderson KD, Largent J, Neuhausen S et al. Risk factors for surgically removed fibroids in a large cohort of teachers. Fertil Steril 2009;92:1436–46. [PubMed: 19019355]
17. Baird DD, Travlos G, Wilson R, Dunson DB, Hill MC, D'Aloisio AA et al. Uterine leiomyomata in relation to insulin-like growth factor-I, insulin, and diabetes. Epidemiology 2009;20:604–10. [PubMed: 19305350]
18. Wise LA, Palmer JR, Stewart EA, Rosenberg L. Polycystic ovary syndrome and risk of uterine leiomyomata. Fertil Steril 2007;87:1108–15. [PubMed: 17241625]
19. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev 1987;8:132–41. [PubMed: 3301317]
20. Incidence Okolo S., aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2008;22:571–88. [PubMed: 18534913]
21. Summers WE, Watson RL, Wooldridge WH, Langford HG. Hypertension, obesity, and fibromyomata uteri, as a syndrome. Arch Intern Med 1971;128:750–4. [PubMed: 4256162]
22. 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]
23. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab 1980;50:113–6. [PubMed: 7350174]
24. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
25. Abdel-Gadir A, Oyawoye OO, Chander BP. Coexistence of Polycystic Ovaries and Uterine Fibroids and Their Combined Effect on the Uterine Artery Blood Flow in Relation to Age and Parity. Journal of Reproductive Medicine 2009;54:347–52. [PubMed: 19639923]
26. Legro RS, Myers ER, Barnhart HX, Carson SA, Diamond MP, Carr BR et al. The Pregnancy in Polycystic Ovary Syndrome study: baseline characteristics of the randomized cohort including racial effects. Fertil Steril 2006;86:914–33. [PubMed: 16963034]
27. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Alvero R et al. The Pregnancy in Polycystic Ovary Syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial. Fertil Steril 2014;101:258–69 e8. [PubMed: 24156957]

28. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P et al. Assessment of multiple intrauterine gestations from ovarian stimulation (AMIGOS) trial: baseline characteristics. Fertil Steril 2015;103:962–73 e4. [PubMed: 25707331]
29. Stewart EA, Cookson C, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG 2017.
30. 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]
31. 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]
32. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551–66. [PubMed: 17287476]
33. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;371:119–29. [PubMed: 25006718]
34. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. N Engl J Med 2015;373:1230–40. [PubMed: 26398071]
35. Legro RS, Schlaff WD, Diamond MP, Coutifaris C, Casson PR, Brzyski RG et al. Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. J Clin Endocrinol Metab 2010;95:5305–13. [PubMed: 20826578]
36. Rein MS, Barbieri RL, Friedman AJ. Progesterone: a critical role in the pathogenesis of uterine myomas. Am J Obstet Gynecol 1995;172:14–8. [PubMed: 7847524]
37. Blake RE. Leiomyomata uteri: hormonal and molecular determinants of growth. J Natl Med Assoc 2007;99:1170–84. [PubMed: 17987921]
38. Moravek MB, Yin P, Ono M, Coon JSt, Dyson MT, Navarro A et al. Ovarian steroids, stem cells and uterine leiomyoma: therapeutic implications. Hum Reprod Update 2015;21:1–12. [PubMed: 25205766]
39. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed) 1986;293:359–62.
40. Nagata C, Nakamura K, Oba S, Hayashi M, Takeda N, Yasuda K. Association of intakes of fat, dietary fibre, soya isoflavones and alcohol with uterine fibroids in Japanese women. Br J Nutr 2009;101:1427–31. [PubMed: 19459228]
41. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL et al. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Hum Reprod 2004;19:1746–54. [PubMed: 15218005]
42. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstetrics & Gynecology 1997;90:967–73. [PubMed: 9397113]

Table 1.

Demographic characteristics of study patients[a].

	PCOS (n=1371)	UI (n=878)	p value[b]
Age, median (IQR), y	28.0 (26.0–31.0)	32.0 (29.0–35.0)	<0.001
BMI, median (IQR), kg/m2	35.0 (28.2–41.3)	25.2 (22.0–30.3)	<0.001
Waist circumference, median (IQR), cm	105.0 (90.2–118.0)	83.0 (75.0–96.0)	<0.001
Waist/hip ratio, median (IQR)	0.88 (0.82–0.93)	0.83 (0.78–0.88)	<0.001
Hispanic or Latino			<0.001
No	78.8 (1080/1371)	89.6 (787/878)	
Yes	21.2 (291/1371)	10.4 (91/878)	
Race			<0.001
Non-Black	85.0 (1165/1371)	91.1 (800/878)	
Black	15.0 (206/1371)	8.9 (78/878)	
Occupation			<0.001
Professional	48.0 (656/1368)	56.3 (494/878)	
Non-professional	52.0 (712/1368)	43.7 (383/878)	
Annual Household income			<0.001
<$50,000	47.4 (633/1334)	16.9 (148/878)	
>=$50,000	44.7 (596/1334)	65.5 (575/878)	
Wish to not answer	7.9 (105/1334)	17.6 (155/878)	
Hirsutism score	15.0 (10.0–21.0)	7.0 (3.0–11.0)	<0.001

IQR, interquartile range.

[a]Data are reported as percentage (no./total no.) unless otherwise indicated.

[b]A Wilcoxon rank sum test was used for testing differences between the two groups for continuous variables; Chi-square or Fisher's exact test was used for categorical variables.

Table 2.

Medical history and lifestyle factors for study patients[a].

	PCOS (n=1371)	UI (n=878)	p value[b]
Length of time trying to conceive, median (IQR), months	24.0 (12.0–60.0)	24.0 (18.0–42.0)	0.674
Prior conception	34.9 (479)	41.5 (364)	0.002
Prior live birth	19.0 (261)	20.4 (179)	0.431
Prior pregnancy loss	22.5 (308)	30.5 (268)	<0.001
Patient had a prior diagnosis of infertility	83.2 (1140)	36.7 (322)	<0.001
Patient had prior therapy for infertility	55.1 (755)	55.0 (483)	0.979
History of thyroid problems	7.4 (102)	8.4 (74)	0.395
History of High blood pressure	5.9 (81)	2.3 (20)	<0.001
History of receiving treatment for any psychiatric conditions	22.2 (304)	22.2 (195)	0.08
Smoking			<0.001
Never	58.9 (808)	65.6 (576)	
Previous	25.2 (346)	26.5 (233)	
Current	15.9 (218)	7.9 (69)	
Alcohol use			<0.001
Never	21.9 (300)	11.4 (100)	
Previous	27.4 (375)	14.8 (130)	
Current	50.8 (696)	73.8 (648)	

IQR, interquartile range.

[a]Data are reported as percentage (no.) unless otherwise indicated.

[b]A Wilcoxon rank sum test was used for testing differences between the two groups for continuous variables; Chi-square or Fisher's exact test was used for categorical variables.

Table 3.

Prevalence of non-cavity-distorting fibroid and largest fibroid volume between study patients.

	Non-cavity-distorting fibroids-no./total no. (%)	P value[a]	Non-cavity-distorting fibroids with any dimension >=4 cm-no./total no. (%)[b]	P value[a]	Largest fibroid volume (cm^3)-median (IQR)[b]	P value[c]
Patient group		<0.001		0.66		0.78
PCOS	92/1371 (6.7)		14/746 (1.9)		6.4 (1.2 – 26.6), n=48	
UI	109/878 (12.4)		14/878 (1.6)		7.6 (1.7 – 29.0), n=99	
Race						
Black		<0.001		1.00		0.26
PCOS	22/206 (10.7)		5/98 (5.1)		40.8 (8.8 – 78.3), n=7	
UI	28/78 (35.9)		4/78 (5.1)		15.6 (6.4 – 31.2), n=26	
Non-Black		0.001		0.82		0.69
PCOS	70/1165 (6.0)		9/648 (1.4)		4.9 (1.0 – 22.4), n=41	
UI	81/800 (10.1)		10/800 (1.3)		4.4 (1.6 – 19.1), n=73	
BMI (kg/m2)						
<25		<0.001		0.59		0.89
PCOS	6/214 (2.8)		0/119 (0)		4.1 (1.7 – 6.4), n=2	
UI	45/425 (10.6)		5/425 (1.2)		3.1 (1.1–19.1), n=42	
25–29		0.02		0.42		
PCOS	12/209 (5.7)		1/125 (0.8)		8.0 (1.7 – 20.7), n=6	0.83
UI	28/218 (12.8)		5/218 (2.3)		12.0 (2.1 – 29.0), n=26	
>=30		<0.001		0.60		0.30
PCOS	74/947 (7.8)		13/502 (2.6)		7.6 (1.1 – 34.1), n=40	
UI	36/235 (15.3)		4/235 (1.7)		11.5 (2.6 – 38.1), n=31	

[a] Chi-square or Fisher's exact test was used.

[b] For patients from PPCOS II and AMIGOS studies only.

[c] A Wilcoxon rank sum test was used.

Table 4.

Adjusted risks of non-cavity-distorting fibroids for study patients[a].

	Adjusted ORs (95% CI)	p value
Patient Group		
UI	Reference	
PCOS	0.54 (0.36–0.79)	0.002
Age (y)	1.16 (1.12–1.21)	<0.001
Waist circumference (cm)	1.01 (1.00–1.02)	0.027
Ethnicity		
Non-Hispanic or Latino	Reference	
Hispanic or Latino	1.58 (1.05–2.39)	0.030
Race		
Non-Black	Reference	
Black	3.02 (2.05–4.46)	<0.001
HOMA-IR	1.02 (1.00–1.04)	0.026
Prior therapy for infertility		
No	Reference	
Yes	1.53 (1.10–2.13)	
Alcohol use		
Never	Reference	
Previous	0.47 (0.29–0.78)	0.003
Current	0.55 (0.37–0.81)	0.002

[a]All variables were introduced to the multivariable regression analysis in a stepwise fashion, using a P value of <.10 to enter and a P value of <.05 to remain.

ORs, Odds ratio; CI, confidence interval. For continuous variables, odds ratio and 95% CI were computed per 1-uint independent variable change.