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RACE AND ETHNICITY DISPARITIES (M. ALBERT, SECTION EDITOR)

Uterine Fibroids, Race, Ethnicity, and Cardiovascular Outcomes

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Abstract

Purpose of Review Uterine fibroids are the cause of significant morbidity for women particularly women of racial and ethnic minorities. This review seeks to draw connections between fibroids and another cause of morbidity and mortality, cardiovascular disease. Fibroids are the most common neoplasm affecting women as well as the most common reason for undergoing hysterectomy. Heart disease is the leading cause of death for women in the USA, and heart disease and stroke disproportionately impact women of racial and ethnic minorities.

Recent Findings Prospective studies in the last several years have revealed a higher prevalence of metabolic syndrome and other clinical and subclinical manifestations of cardiovascular disease in women with fibroids.

Summary Study of the clinical and subclinical manifestations of each disease state may set the foundation for both preventative and therapeutic interventions.

Keywords Uterine fibroids · Race · Ethnicity · Leiomyomas · Cardiovascular disease · Perceived stress

Abbreviations

BMI	Body mass index
BWHS	Black Women's Health Study
CVD	Cardiovascular disease
MI	Myocardial infarction
NSQIP	National Surgical Quality Improvement Program

Introduction

Heart disease and cerebrovascular disease (CVD or "stroke") are consistently among the top ten leading causes of death in the USA [1]. Interestingly, cardiovascular disease and fibroids, the most common benign tumor found in women, are often comorbidities within the same patient. A systematic review of the epidemiology of uterine fibroids including cohorts such as the Black Women's Health Study (BWHS), the Women's Health Study, the Nurses' Health Study II, and the California Teachers Study found that the incidence of fibroids among Black women was three times higher than that in White, Hispanic, and Asian women (see Fig. 1) [2]. The number one risk factor for cardiovascular disease, hypertension, is more prevalent in Black women with fibroids. There are clear racial and ethnic disparities in the incidence of fibroids and cardiovascular disease. As we explore the racial and ethnic disparities in fibroids and cardiovascular outcomes, it is important to dissociate race from genetics and consider racism, psychosocial and socioeconomic status, and the impact of oxidative stress on these disease processes [3]. Understanding the burden of fibroids and cardiovascular disease among racial and ethnic minorities may set the foundation for novel preventative and therapeutic options.

Epidemiology

Uterine fibroids, also known as leiomyomas or myomas, are benign (non-cancerous) smooth muscle tumors of the myometrium, the muscle layer of the uterus (see Fig. 2) [4].

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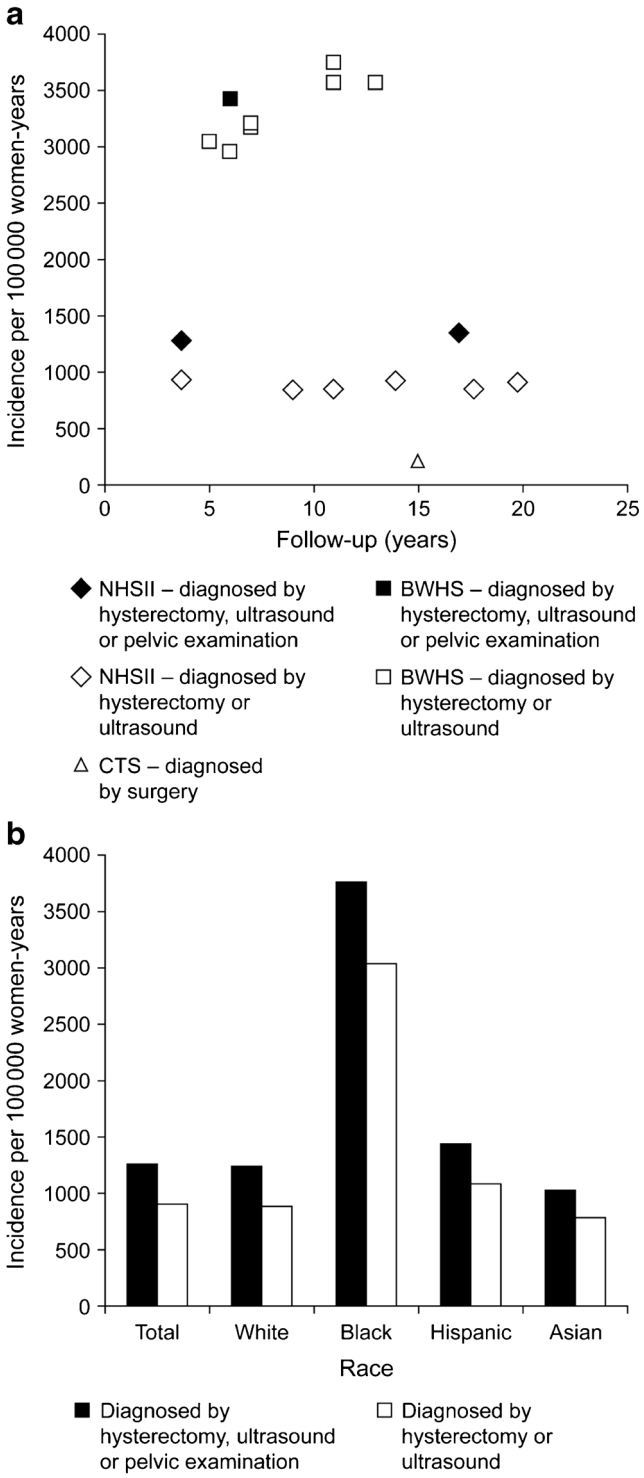

Fig. 1 Incidence of fibroids. **a** Incidence in US registry studies. **b** Incidence of uterine fibroids according to race in the Nurses' Health Study II. *BWHS* Black Women's Health Study, *CTS* California Teachers Study, *NHSII* Nurses' Health Study II (Stewart et al. [2])

Fibroids occur in 70–80% of women by the age of fifty. Twenty-five percent of those fibroids are symptomatic causing heavy menses and other abnormal uterine bleeding, bulk symptoms due to size, and compression on adjacent organs such as the bowel, bladder, and nerves of the pelvis [5]. Fibroids located within or adjacent to the endometrium, submucosal fibroids, can impact fertility and cause more uncontrolled bleeding. Black women have a greater burden of disease when compared with White women—fibroids are larger and more numerous. In addition, a study of 72 premenopausal women with 262 fibroids among them found that growth rates for fibroids declined with age for White women, but not for Black women, which may explain the higher burden of disease in Black women [6].

Besides Black race, other major risk factors for fibroids include age, family history, time since last birth (specifically greater than 5 years), premenopausal status, hypertensive disease, and consumption of food additives and soybean milk. Protective factors include smoking status in women with low body mass index (BMI) less than 22 kg/m^2, increased parity, and use of oral and injective contraceptives such as depot medroxyprogesterone acetate (Depo Provera). These factors, whether causative or protective, are largely based on the relative exposure to ovarian or peripheral hormone production such as from steroid conversion to estrogen in obese patients. For example, smoking can have anti-estrogenic properties, and parity and hormonal contraceptives disrupt the cyclic hormonal milieu and unopposed estrogen.

Pathophysiology

A combination of gonadal steroids, hypoxia, and angiogenic growth factors are involved in the development of leiomyoma from progenitor myometrial cells (see Fig. 3) [7]. A similar process is involved in the smooth muscle development in blood vessels. Several theories of the association of fibroids and cardiovascular disease have been proposed, though both disease processes are multifactorial. This connection was first noted in the early 1970s when Moss and Benditt noted that fibroids and atherosclerotic plaques have similar properties in vitro [8]. Silver et al. proposed that cardiac and uterine smooth muscles are similarly modulated by angiotensin II, a hormone that regulates vascular tone, and can promote cell growth and endothelial cell abnormalities which are seen in both cardiac disease and uterine fibroids [9]. Other studies point to global abnormalities in the synthesis of the extracellular matrix in fibroids which is a correlate for plaque formation in blood vessels [10, 11]. It has also been proposed that estrogens, IGF-I and insulin, and leptin facilitate development of metabolic syndrome as well as several gynecologic disorders including fibroids [12].

Management

Both qualitative and quantitative studies demonstrate racial and ethnic disparities in the management,

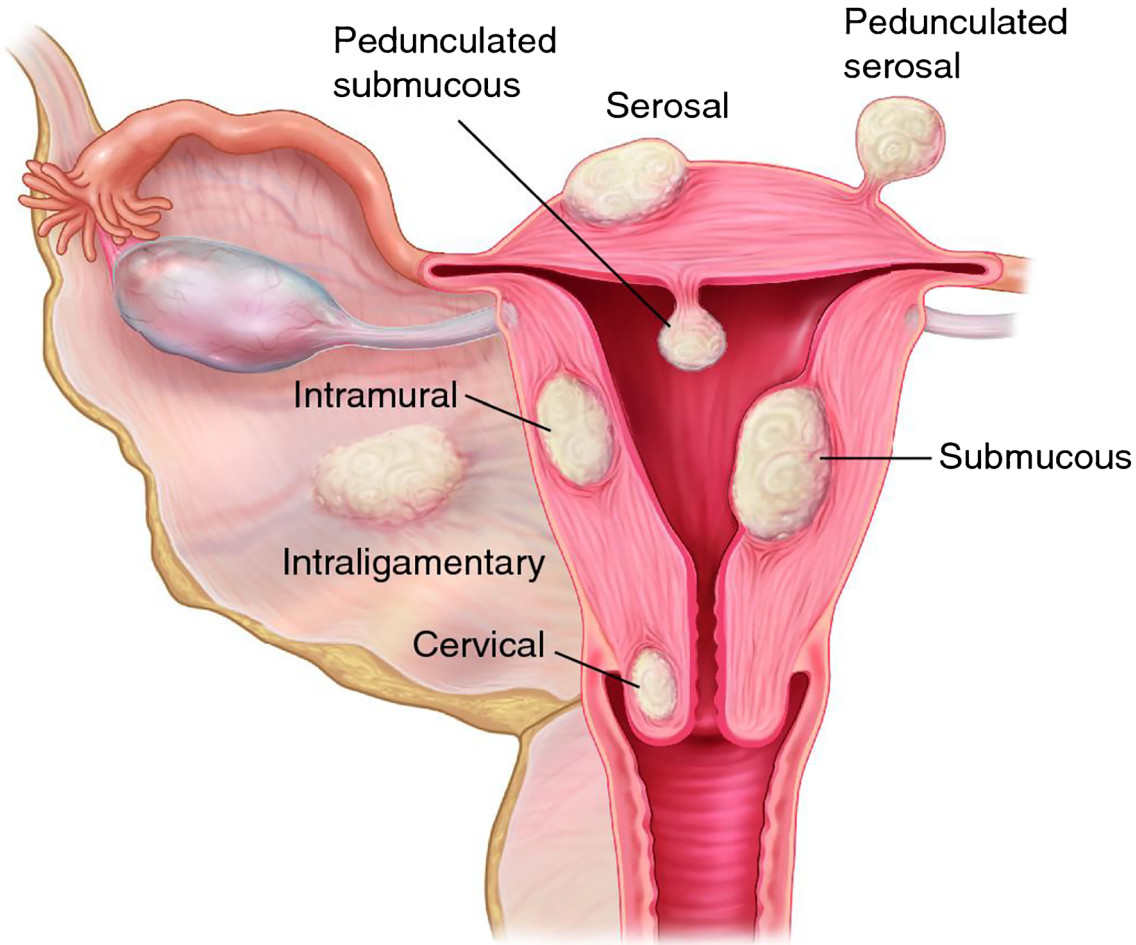

Fig. 2 Types of leiomyomas [4]

experience, and actual treatment provided between Black women and women of other racial and ethnic groups. A qualitative study involving semi-structured one-on-one interviews of 60 study participants found that African-American women were more likely to report high treatment expectations, incomplete counseling, financial challenges, and dissatisfaction with treatment outcomes [13]. Of note, the voluntary study cohort included 61.7% African-American, 25% White, 8.3% Hispanic, and 5.0% Asian women [13].

A larger cohort study using the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) questionnaire and Aberdeen Menorrhagia Severity Scale (AMSS) found that Hispanic women reported greater symptom severity when compared with White and Black women [14].

Treatment options for uterine fibroids include expecta management of symptoms, hormonal and non-hormonal medical therapy, uterine-sparing procedures, and definitive management via hysterectomy. Hysterectomy is the second most common surgical procedure performed on women in the USA and is most commonly indicated for uterine fibroids [15]. Hysterectomy can be performed using minimally invasive gynecologic procedures, or a larger incision (an open/abdominal approach). Minimally invasive techniques are advantageous due to decreased length of surgery, length of stay in hospital, more rapid return to baseline functional status, and decreased infection and other perioperative complications. In a cross-sectional study of 1746 hysterectomies performed for fibroids or abnormal uterine bleeding at 3 academic-affiliated hospitals in Philadelphia, Hispanic ethnicity and Medicaid enrollment were associated with lower odds of treatment with minimally invasive hysterectomy (vaginal, laparoscopic, or robotic-assisted laparoscopic approach) [16]. A cohort study of over 15,000 hysterectomies performed for benign indications recorded in the 2015 National Surgical Quality Improvement Program (NSQIP) found that Black women were more likely to undergo open hysterectomy and have more major and minor complications compared with White women when controlling for confounding factors such as uterine size, prior pelvic surgery, and BMI [17].

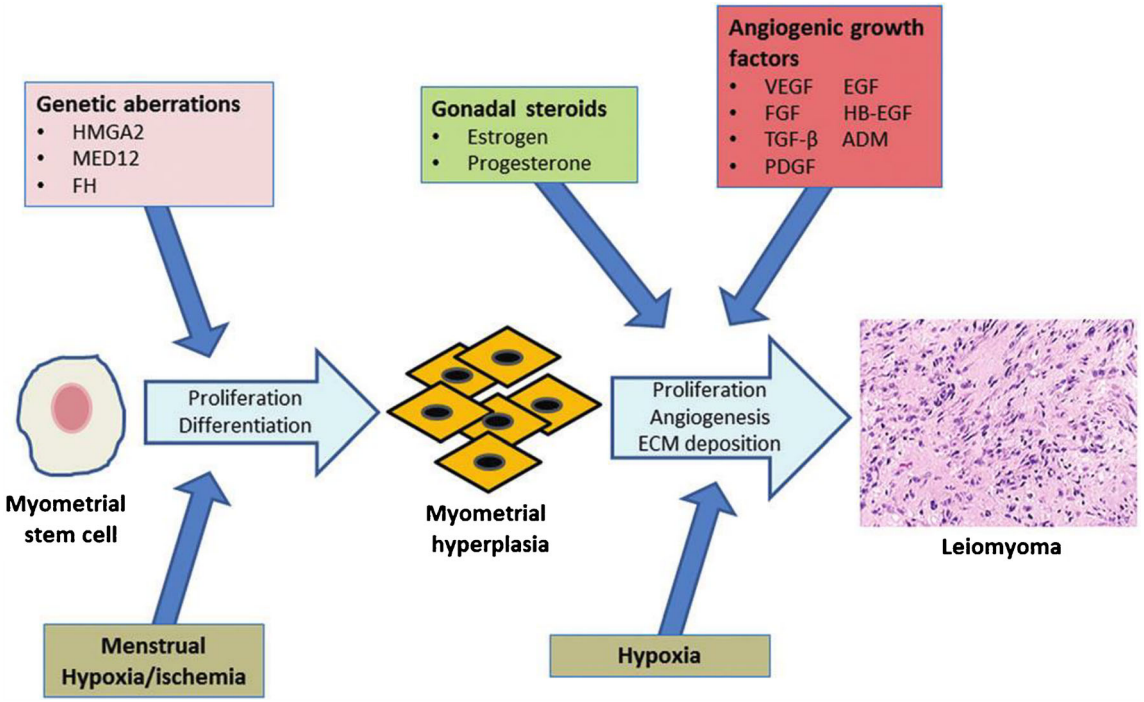

Fig. 3 Leiomyoma development. Genetic aberrations in HMGA2, MED12, and FH facilitate unregulated cell proliferation of myometrial stem cells. Normal changes in the myometrium during the menstrual cycle lead to hypoxia causing differentiation of myometrial stem cells into smooth muscle cells. This cycle leads to myometrial hyperplasia and stimulates angiogenic growth factor expression. These promote further cell proliferation and deposition of extracellular matrix and provide support for leiomyoma formation. *HMGA2*, high-mobility group AT-hook 2 protein; *MED12*, mediator subunit complex 12; *FH*, fumarate hydratase; *ADM*, adrenomedullin (Tal and Segars [7])

Cardiovascular Disease and Fibroids

As previously stated, the origin of the relationship between cardiovascular status and fibroids has not been well elucidated. Multiple studies have supported a correlation between the two phenomena; however, it is not clear if one process precedes the other.

Many studies have supported a strong correlation between the presence of fibroids and a diagnosis of some form of cardiovascular disease. In a recent cross-sectional study, Haan et al. showed that women with fibroids have higher blood pressures, higher plasma glucose, and more asymptomatic organ damage measured by arterial stiffness, left ventricular hypertrophy, or reduced kidney function (either GFR < 60 ml/min/1.73 m^2 or proteinuria) [18••]. A prospective analysis of the relationship between blood pressure and fibroids demonstrated that the risk of fibroids increased by 8% with 10 mmHg interval increases in diastolic blood pressure. That risk was even higher for patients not being treated with antihypertensives [19]. Aksoy et al. demonstrated that patients with a diagnosis of uterine fibroids were more likely to have increased carotid intima-media thickness and decreased HDL, both markers for atherosclerosis. Among patients with fibroids, patients on statins were more likely to display a lower intima-media thickness [20]. Similarly, Korkmaz et al. showed women with fibroids were more likely to have a deranged lipid profile, insulin resistance, and increased carotid intima-media thickness [21]. A survey and registry search of over three thousand women in Finland demonstrated a significantly increased risk of uterine fibroids with higher waist to hip ratio, impaired glucose tolerance, and metabolic syndrome in all studied cases of uterine fibroids. The association was stronger in cases that were ICD-code confirmed [22••]. Laughlin-Tommaso et al. compared the incidence of cardiovascular risk factors and subclinical evidence of coronary artery disease in women with fibroids and those without in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Although consistent with prior knowledge, women with fibroids had a higher incidence of cardiovascular risk factors such as obesity and hypertension, they saw no difference in subclinical markers of CVD over 10 years of follow-up [23].

Hysterectomy itself is likely a risk factor for cardiovascular disease [24, 25]. Though data has been conflicting, a longitudinal study of women for an average of 22 years showed that women who underwent hysterectomy were at increased risk of developing hyperlipidemia, hypertension, cardiac arrhythmias, and coronary artery disease in the post-operative period. Younger women seem to be at even higher risk of developing these diseases [26]. Most hysterectomies are now performed with ovarian conservation particularly in premenopausal women undergoing hysterectomy for benign indications.

The presence of ovaries provides protection against cardiovascular and neurologic disease; however, studies have shown that patients were more likely to develop hypertension after oophorectomy [27]. This appears to be even higher in patients who have their ovaries removed at the time of hysterectomy. Laughlin-Tommaso et al. found that women undergoing hysterectomy with ovarian conservation for fibroids compared with matched controls who did not have a hysterectomy were more likely to have obesity in multivariate analysis. Other cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and metabolic syndrome were not significantly different between the two groups [28].

Minority Stress, Cardiovascular Disease, and Fibroids

Minority stress is a phenomenon of a minority group being exposed to multiple psychological stressors subsequently leading to poorer health outcomes [29]. It is well known that African-Americans are at disproportionally higher risk of cardiovascular disease. African-American women have been found to report higher perceived stress and major life events when compared with women of other races [30]. The effects of these perceived stressors have been demonstrated to have effects at the level of gene expression. Hellwege et al. showed an increased frequency of alleles that have a role in fibroproliferative diseases such as fibroids and atherosclerosis in those of African descent [31]. It has also been shown that pro-inflammatory cytokines and cortisol are elevated in African-American women with higher levels of perceived stress [32–34].

An analysis from the Women's Health Study follow-up cohort used a composite score of acute and chronic stressors called the cumulative stress score which incorporates multiple domains of stress over time. This score showed that African-American women had higher rates of chronic perceived stress such as stress from interpersonal relationships, work, and environment and less than ideal cardiac health scores when compared with White and Asian women. These results were unchanged when comparing acute and chronic stressors indicating an even more complex relationship between stress and cardiovascular health [35]. Saban et al. used resilience as a possible marker for improving cardiovascular health. They defined resilience as the confluence of psychosocial, cultural, and biological factors that facilitate an individual's ability to respond to stressful incidents. Multiple factors in a woman's life may confer resilience; however, in this study, the rate of cardiovascular disease in African-American women was found to be decreased in women who perceived that they had good social support and had good social status compared with their peers [36].

Data from the BWHS demonstrated that, among Black women who reported more perceived stress, fibroids were more likely to be confirmed on ultrasound or during surgical procedure [37]. A previous study exploring the effect of stress on fibroids showed that African-American women were more likely to report a major life event and more likely to be diagnosed with fibroids compared with their White counterparts [30]. While not yet well understood, the link between perceived psychological stressors and their negative impact on cardiovascular health is indirectly linked to fibroid development. It is likely that, similarly to cardiovascular disease progression, psychosocial stress, whether perceived or actual, initiates an inflammatory pathway and increases morbidity in women with uterine fibroids.

Conclusions

> If you check the health of a woman, that's the health of a society.
> - Chimamanda Adichie

Women continue to be a marker of the overall health of a society, and specific gynecologic conditions are increasingly becoming gateways for screening for cardiovascular disease. The January 2019 American College of Obstetrics and Gynecology (ACOG) Practice Bulletin, Gestational Hypertension and Preeclampsia, discusses a doubling of future risk of cardiovascular disease after the affected pregnancy [38]. Similarly, gestational diabetes mellitus is a well-known risk factor for type II diabetes mellitus and subsequent cardiovascular disease. Polycystic ovarian syndrome (PCOS) is associated with metabolic syndrome and is also a known risk factor for cardiovascular disease. Fibroids may prove to be another gynecologic risk factor for cardiovascular disease. Improved understanding of the comorbidities of fibroids and cardiovascular disease in Black and other racial and ethnic minorities will improve preventive and therapeutic options for both diseases. Further study is needed in the areas of psychosocial and oxidative stress to understand the racial and ethnic underpinnings of fibroid and cardiovascular disease.

Compliance with Ethical Standards

Conflict of Interest Nyia L. Noel is a consultant for OBP Medical. Paul Hendessi is a consultant for Medtronic. Alexis Gadson declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Chang M-H, Moonesinghe R, Athar HM, Truman BI. Trends in disparity by sex and race/ethnicity for the leading causes of death in the United States-1999-2010. J Public Health Manag Pract. 2016;22(Suppl 1):S13–24.
2. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG An Int J Obstet Gynaecol. 2017;124:1501–12.
3. Ghidei L, Murray A, Singer J. Race, research, and women's health: best practice guidelines for investigators. Obstet Gynecol. 2019;133:815–8.
4. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM (2016) Pelvic mass. Williams Gynecol. 3e.
5. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188:100–7.
6. Peddada SD, Laughlin SK, Miner K, Guyon JP, Haneke K, Vahdat HL, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A. 2008;105:19887–92.
7. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update. 2014;20:194–216. https://doi.org/10.1093/humupd/dmt042.
8. Moss NS, Benditt EP. Human atherosclerotic plaque cells and leiomyoma cells. Comparison of in vitro growth characteristics. Am J Pathol. 1975;78:175–90.
9. Silver MA, Raghuvir R, Fedirko B, Elser D. Systemic hypertension among women with uterine leiomyomata: potential final common pathways of target end-organ remodeling. J Clin Hypertens (Greenwich). 2005;7:664–8.
10. Malik M, Norian J, McCarthy-Keith D, Britten J, Catherino WH. Why leiomyomas are called fibroids: the central role of extracellular matrix in symptomatic women. Semin Reprod Med. 2010;28:169–79.
11. Leppert PC, Catherino WH, Segars JH. A new hypothesis about the origin of uterine fibroids based on gene expression profiling with microarrays. Am J Obstet Gynecol. 2006;195:415–20.
12. Settnes A, Andreasen AH, Jørgensen T. Hypertension is associated with an increased risk for hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2005;122:218–24.
13. Sengoba KS, Ghant MS, Okeigwe I, Mendoza G, Marsh EE. Racial/ethnic differences in women's experiences with symptomatic uterine fibroids: a qualitative assessment. J racial Ethn Heal disparities. 2017;4:178–83.
14. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, prevalence, and treatment of uterine fibroids: a survey of U.S. women. J Women's Health (Larchmt). 2018;27:1359–67.
15. Wright JD, Herzog TJ, Tsui J, Ananth CV, Lewin SN, Lu Y-S, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol. 2013;122:233–41.
16. Price JT, Zimmerman LD, Koelper NC, Sammel MD, Lee S, Butts SF. Social determinants of access to minimally invasive hysterectomy: reevaluating the relationship between race and route of hysterectomy for benign disease. Am J Obstet Gynecol. 2017;217:572.e1–572.e10.
17. Alexander AL, Strohl AE, Rieder S, Holl J, Barber EL. Examining disparities in route of surgery and postoperative complications in black race and hysterectomy. Obstet Gynecol. 2019;133:6–12.
18.•• Haan YC, Diemer FS, Van Der Woude L, Van Montfrans GA, Oehlers GP, Brewster LM. The risk of hypertension and cardiovascular disease in women with uterine fibroids. J Clin Hypertens. 2018;20:718–26 **Haan et al. performed a cross-sectional study of women with self-reported fibroids. They demonstrated that women with fibroids were 3.4 times more likely to have hypertension, 1.7 times more likely to have diabetes, and 1.8 times more likely to have hypercholesterolemia. When adjusted for confounders, women remained 1.8 times more likely to develop hypertension if they had fibroids as well. Asymptomatic end organ damage occurred significantly more often in younger women with fibroids.**
19. Boynton-Jarrett R, Rich-Edwards J, Malspeis S, Missmer SA, Wright R. A prospective study of hypertension and risk of uterine leiomyomata HHS public access. Am J Epidemiol. 2005;161:628–38.
20. Aksoy Y, Sivri N, Karaoz B, Sayin C, Yetkin E. Carotid intima-media thickness: a new marker of patients with uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol. 2014;175:54–7.
21. Korkmaz V, Ozkaya E, Özer Kadife S, Kara F, Kucukozkan T. Investigation of cardiovascular disease risk in women with uterine leiomyomas. Ir J Med Sci. 2016;185:689–93.
22.•• Uimari O, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, Järvelin M-R, et al. Uterine fibroids and cardiovascular risk. Hum Reprod. 2016;31:2689–703 **Uimari et al. performed an analysis of a long-term Finnish cohort followed for 45 years. They correlated incremental increases in LDL and cholesterol levels with increased risk of diagnosis of fibroids. They also noted an increased risk of fibroids with increased waist-hip ratio. A diagnosis of metabolic syndrome increased risk of diagnosis of fibroids.**
23. Laughlin-Tommaso SK, Fuchs EL, Wellons MF, Lewis CE, Calderon-Margalit R, Stewart EA, et al. Uterine fibroids and the risk of cardiovascular disease in the coronary artery risk development in young adult women's study. J Women's Health. 2018;28:46–52.
24. Radin RG, Rosenberg L, Palmer JR, Cozier YC, Kumanyika SK, Wise LA. Hypertension and risk of uterine leiomyomata in US black women. Hum Reprod. 2012;27:1504–9.
25. Ding D-C, Tsai I-J, Hsu C, Wang J-H, Lin S-Z, Sung F-C. Risk of hypertension after hysterectomy: a population-based study. BJOG An Int J Obstet Gynaecol. 2018;125:1717–24.
26. Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation. Menopause. 2017;25:1.
27. Erekson EA, Martin DK, Ratner ES. Oophorectomy: the debate between ovarian conservation and elective oophorectomy. Menopause. 2013;20:110–4.
28. Laughlin-Tommaso SK, Khan Z, Weaver AL, Schleck CD, Rocca WA, Stewart EA. Cardiovascular risk factors and diseases in women undergoing hysterectomy with ovarian conservation. Menopause. 2016;23:121–8.
29. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129:674–97.
30. Vines AI, Ta M, Esserman DA. The association between self-reported major life events and the presence of uterine fibroids. Womens Health Issues. 2010;20:294–8 [1].
31. Hellwege JN, Torstenson ES, Russell SB, Edwards TL, Velez Edwards DR. Evidence of selection as a cause for racial disparities in fibroproliferative disease. PLoS One. 2017;12:e0182791.
32. Saban KL, Mathews HL, Bryant FB, Tell D, Joyce C, DeVon HA, et al. Perceived discrimination is associated with the inflammatory response to acute laboratory stress in women at risk for cardiovascular disease. Brain Behav Immun. 2018;73:625–32.
33. Cunningham TJ, Seeman TE, Kawachi I, Gortmaker SL, Jacobs DR, Kiefe CI, et al. Racial/ethnic and gender differences in the association between self-reported experiences of racial/ethnic

discrimination and inflammation in the CARDIA cohort of 4 US communities. Soc Sci Med. 2012;75:922–31.
34. Korous KM, Causadias JM, Casper DM. Racial discrimination and cortisol output: a meta-analysis. Soc Sci Med. 2017;193:90–100.
35. Burroughs Peña MS, Mbassa RS, Slopen NB, Williams DR, Buring JE, Albert MA. Cumulative psychosocial stress and ideal cardiovascular health in older women. Circulation. 2019;139:2012–21.
36. Saban KL, Tell D, Janusek L. Resilience in African American women at risk for cardiovascular disease: an exploratory study. J Urban Heal. 2019;96:44–9.
37. Wise LA, Palmer JR, Cozier YC, Hunt MO, Stewart EA, Rosenberg L. Perceived racial discrimination and risk of uterine leiomyomata. Epidemiology. 2007;18:747–57.
38. Vidaeff A, Pettker CM, Simhan H. Gestational hypertension and preeclampsia ACOG PRACTICE BULLETIN. Clinical Management Guidelines for Obstetrician-Gynecologists Am Coll Obstet Gynecol. (2019);133:1–25.