UTERINE LOCATION OF LEIOMYOMATA: RISK FACTORS AND RELATION TO STRESS URINARY INCONTINENCE

Anca Dana Dragomir

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2007

Approved by:

Jane Schroeder, Advisor

Donna Baird, Reader

Andrew Olshan, Reader

AnnaMarie Connolly, Reader

Lawrence Kupper, Reader

ABSTRACT

ANCA DANA DRAGOMIR: Uterine Location of Leiomyomata:
Risk Factors and Relation to Stress Urinary Incontinence
(Under the direction of Jane Schroeder)

The first objective of this research was to compare risk factors for three uterine leiomyomata (UL) subtypes (submucosal UL, intramural/subserosal UL, and diffuse only) among African-American and Caucasian women. The second objective was to investigate the association between UL and self-reported SUI in premenopausal women. Data were from 35 to 49 year old premenopausal African American and Caucasian women enrolled in the National Institute of Environmental Health Sciences Uterine Fibroid Study.

The cross-sectional study of risk factors for UL subtypes included 986 premenopausal women (581 African-American, 405 Caucasian). For women in both ethnic groups, associations with age at ultrasound examination, age at menarche, body mass index, and current physical activity were similar for all three UL subtypes. Inverse associations estimated for pregnancies after age 24 were stronger for the submucosal UL subtype than the other two subtypes. Current smoking was positively associated with the diffuse only subtype, but was not associated with focal UL subtypes in either ethnic group.

The study of UL and SUI included 798 premenopausal women (446 African-American and 352 Caucasian). The estimated prevalence of SUI was higher among women with UL than among women without UL. Associations were slightly stronger for medium (2-4cm) and large (≥ 4cm) UL, but anterior location was not associated with further increase in

prevalence. Women with very large uterine volume (above the 83rd percentile for the population) reported more SUI than those with small uterine volume (bellow the 33rd percentile). There was no clear evidence of effect modification by ethnicity or parity.

The two studies have improved upon prior research by identifying and characterizing UL based on ultrasound examinations (instead of including diagnosed UL only), and by including both African American and Caucasian women. Results suggest that future studies of UL etiology should distinguish the focal UL subtypes from the diffuse only subtype to account for potential differences in etiologic mechanisms, and that treatment for larger UL might enhance SUI treatment in some women.

ACKNOWLEDGEMENTS

I want to thank Dr. Jane Schroeder and Dr. Donna Baird for their extraordinary support and guidance. Their encouragement, dedication, and expertise made it possible for me to pursue and complete this research work. I would also like to thank Dr. AnnaMarie Connolly, Dr. Andrew Olshan, and Dr. Lawrence Kupper for their insightful comments and valuable suggestions. Many thanks also to Dr. Dale Sandler who was always supportive and gave me great advice when I needed it. I am thankful to my husband George and my son Alex for their love, encouragement, and patience throughout this long and difficult journey.

This research has been carried out while being an Intramural Research Training Award predoctoral fellow at the National Institute of Environmental Health Sciences.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

ABBREVIATIONS

aOR	Adjusted Odds Ratio
aPD	Adjusted Prevalence Difference
BMI	Body Mass Index
CI	Confidence Interval
NIEHS	National Institute of Environmental Health Sciences
OR	Odds Ratio
PD	Prevalence Difference
SUI	Stress Urinary Incontinence
UFS	Uterine Fibroid Study
UL	Uterine Leiomyomata

CHAPTER I

REVIEW OF THE LITERATURE

Introduction

Uterine leiomyomata (UL) are the most prevalent tumors of women in the United States (Flake et al. 2003). Based on cross-sectional screening for UL done among women aged 35 to 49 years old without regard to the presence or absence of clinical symptoms, the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study estimated that more than 80% of African-American women and about 70% of Caucasian women develop UL by age 50 (Baird et al. 2003). Although only about 20% to 50% of women with UL experience related symptoms (Stovall 2001), the economic impact of UL is considerable. Estimates for the direct cost of treating UL have been as high as $2.1 billion per year (Flynn et al. 2006).

Epidemiological studies tend to investigate risk factors associated with the presence of UL without regard to anatomic location, whereas studies that have evaluated the association of characteristics of UL with reproductive outcomes have noted that anatomic location could be an important predictor of adverse effects. Thus there is a need to identify risk factors associated not only with the presence of UL in general, but also with their presence at specific location.

No population-based epidemiological studies have investigated risk factors for the location of UL. The association of age at first birth with the location of UL has been examined only as a secondary analysis in a practice-based case-control study, in which the

results were limited by the small number of women with known location of UL (Faerstein et al. 2001 a). The proposed research will investigate risk factors for the location of UL using premenopausal African-American and Caucasian women from the baseline data of the NIEHS Uterine Fibroid Study for whom the location of their UL is known.

Urinary incontinence is one of the most common types of lower urinary tract dysfunction, affecting about a third of adult women in the United States (DuBeau 2001). The annual direct cost of urinary incontinence for women in the US is estimated as $12.4 billion (in 1995 dollars) (Wilson et al. 2001).

Stress urinary incontinence (SUI), i.e. the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing (Abrams et al. 2002), is the most common type of urinary incontinence in women, with about half of women with urinary incontinence suffering from SUI (Hampel et al. 1997). SUI accounts for 85% of treatment expenditures for urinary incontinence for women (Wilson et al. 2001), and also may have a substantial negative impact on the quality of life (Contreras-Ortiz 2004).

Although it is often stated in the literature that UL and SUI are associated (Stovall 2001, Nygaard and Heit 2004) there is little evidence to support it. No population-based observational studies have assessed the association between the size and location of UL and SUI. The proposed research will fill this research gap based on data from African-American and Caucasian premenopausal women from the first follow-up of the NIEHS Uterine Fibroid Study.

Epidemiology of Uterine Leiomyomata

UL are the most prevalent tumors of women in the United States (Flake et al. 2003). These benign neoplasms are monoclonal, arise from the smooth-muscle cells of the uterus, and contain an increased amount of extracellular matrix proteins, such as collagen and elastin (Stewart 2001, Walker and Stewart 2005). Regarding their gross features, UL are firm, rubbery, and are characterized by a very sharp line of demarcation between them and the surrounding myometrium (Robboy et al. 2000).

Although the prevalence of UL was estimated to be as high as 77% in hysterectomy specimens (Cramer and Patel 1990), perhaps only about 20% to 50% of women with UL experience related symptoms (Stovall 2001). Several epidemiological studies have found that African-American women are more likely than Caucasian women to have multiple UL, larger diameter UL, and greater uterine weight (Kjerulff et al. 1996, Marshall et al. 1997). Based on cross-sectional screening for UL done among women aged 35 to 49 years old without regard to the presence or absence of clinical symptoms, the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study estimated that more than 80% of African-American women and about 70% of Caucasian women develop UL by age 50 (Baird et al. 2003). If attention is restricted to clinically relevant UL (defined as the presence of an enlarged uterus, or the presence of a tumor with a diameter of at least 4 cm, or the presence of submucous UL) approximately 50% of African-American and 35% of Caucasian premenopausal women will have clinically relevant UL by age 50.

Although a large percentage of the women with UL are asymptomatic, the economic impact of UL is considerable. From 1988 to 1990 UL was one of the five most common hospital discharge diagnoses among all gynecologic disorders for reproductive-age women

(Velebil and al. 1995). From 1990 to 1997 about 40% of total abdominal hysterectomies, and about half of subtotal hysterectomies were performed for UL (Farquhar and Steiner 2002). From 1994 through 1999 UL was the most frequent diagnosis for the approximately 600,000 hysterectomies performed annually in the United States (Keshavarz et al. 2002). Estimates for the direct cost of treating UL have been as high as $2.1 billion per year (Myers et al. 2001).

UL are heterogeneous with respect to their natural history. Etiology is believed to involve the combined effect of risk factors (such as ethnicity, parity, obesity) and genetic alterations (including hereditary susceptibilities and somatic alterations) acting through hormones (estrogen and progesterone) and growth factors (Walker and Stewart 2005).

A recent comprehensive review on the epidemiology of UL (Schwartz 2001) summarized the results of 20 papers published between 1986 and 2001 that were based on data from 11 epidemiological studies. The review emphasizes that many of these studies have important methodological limitations, the most critical being limitations due to the presence of subclinical UL among women without established clinical disease, and the use of case identification via hysterectomy. Because of the latter, women who have not been treated for their UL often have not been included as cases, and even when case status is based on a clinical diagnosis of UL there may be substantial misclassification of case/control status because of undiagnosed UL.

Of the 11 epidemiological studies cited only two were specifically designed to identify risk factors for UL, one in Thailand (Lumbiganon et al. 1996) and the other in the United States (Faerstein et al. 2001 a, Faerstein et al. 2001 b). Most of the studies were conducted as ancillary investigations within larger studies of women's reproductive health,

such as the Oxford Family Planning Association Study (Ross et al. 1986), the Cancer and Steroid Hormone Study (Samadi et al. 1996), and the Nurses' Health Study (Marshal et al. 1997). Five of the studies were cohort studies, while the other six were case-control studies, including the two studies that focused on UL etiology. Overall most of the participants in these studies were Caucasian premenopausal women.

Schwartz's review underlines the consistency of results for ethnicity, age at menarche, postmenopausal status, parity, years since last birth, and cigarette smoking, while inconsistent results were noted for use of oral contraceptives, history of infertility, and BMI (Schwartz 2001). There were also risk factors that were investigated by too few studies to provide conclusive evidence, such as the use of an injectable progestin-only contraceptive (Lumbiganon et al. 1996), diet (Chiaffarino et al. 1999), family history (Lumbiganon et al. 1996), perineal talc use (Faerstein et al. 2001 b), and use of antihypertensive medication (Faerstein et al. 2001 b). In addition there is also evidence that risk factors for UL may vary by ethnicity (Chen et al. 2001).

Table 1.1 contains the 20 papers reviewed in Schwartz (2001) and nine more recent papers not included in that review. The nine epidemiological papers published since 2001 include six based on the Black Women's Health Study and the NIEHS Uterine Fibroid Study, two studies that included African-American women. The three papers that used prospective data from the Black Women's Health Study provide evidence supporting the role of age at menarche, parity, years since last birth, BMI, age at first birth, current use of progestin-only injectables, and alcohol consumption, among African-American women (Wise et al. 2004 a, Wise et al. 2004 b, Wise et al. 2005). Without reporting estimates for the effect of smoking on UL, all three papers included adjustment for smoking. These data also suggest that among

African-American women the inverse association between parity and UL is attenuated by obesity, such that the inverse relationship was stronger among those with BMI < 27 (below the median) (Wise et al. 2004 a). The most recent paper (Wise et al. 2005) described different relationships between BMI and UL (self-reported, ultrasound or hysterectomy-diagnosed cases), one for the parous and the other for the nulliparous premenopausal African-American women.

Based on cross-sectional data from the NIEHS Uterine Fibroid Study, which included both African-American and Caucasian women, it was shown that prenatal diethylstilbestrol exposure is associated with UL (Baird and Newbold 2005) and that luteinizing hormone may stimulate UL development in premenopausal women (Baird et al. 2006). Also the number of full-term pregnancies after age 24, physical activity, and alcohol consumption have been found to be associated with UL (D'Aloisio and Baird 2004, Baird et al. 2006).

Prospective data from the Nurses' Health Study (Boynton-Jarrett et al. 2005) suggest that hypertension is a risk factor for UL, consistent with previous results (Faerstein et al. 2001 b). Maternal history of UL was strongly associated with UL in a small hospital-based case-control study involving mostly Caucasian women (Van Voorhis et al. 2002). The use of estrogen and progestogen therapy was associated with UL among perimenopausal and postmenopausal women with lower BMI (BMI < 24) in a recent case-control study of mostly Caucasian women (Reed et al. 2004).

In summary, the reviewed literature underlines the importance of ethnicity, postmenopausal status, age at menarche, parity, cigarette smoking, BMI, physical activity, and alcohol consumption, as risk factors for UL.

Location of Uterine Leiomyomata

Based on their location, UL are classified as submucosal, intramural, and subserosal. Submucosal UL intrude in, or are contained in, the endometrial cavity; intramural UL are contained within the wall of the uterus; and subserosal UL extend the uterus into the peritoneal cavity (Stewart 2001). According to the literature, intramural UL are the most common (Robboy et al. 2000, Walker and Stewart 2005). For example, in an ultrasound study of UL in pregnancy involving 408 women aged 23 to 43 years old, 281 (69%) women were classified as having intramural UL, 75 (18%) women had subserosal UL, and only 52 (13%) women had submucosal UL (Rosati et al 1989).

There is available scientific evidence of differences between submucosal, intramural, and subserosal UL, that extend beyond their anatomic location. Pathophysiological data suggest that submucosal UL, which arise from the highly specialized structure of the junctional zone myometrium, are distinct clinical entities from other UL (Brosens 2003). A cytogenetic study that investigated the presence of chromosomal aberrations in 217 UL using cytogenetic karyotyping found that the prevalence of abnormal karyotypes among submucosal UL (12%) was significantly smaller than among intramural UL (35%) or subserosal UL (29%), after adjusting for the size of UL (Brosens et al. 1998). Using uteri obtained from 30 women undergoing hysterectomy for UL, a laboratory study found that during the proliferative phase of the menstrual cycle, estrogen receptor and progesterone receptor levels were significantly higher in submucosal UL (n=5) than in subserosal UL (n=5) (Marugo et al. 1989). Receptor levels were also significantly higher in submucosal UL (n=9) than in subserosal UL (n=9) in the secretive phase of the menstrual cycle.

The choice among various surgical techniques to deal with UL, and the outcome of various infertility treatment options, are strongly dependent on the anatomical location of UL. Pregnancy and implantation rates were significantly lower in patients with submucosal and intramural UL in a study of the effect of the location of UL on the outcome of assisted reproductive technology treatment (Eldar-Geva et al. 1998). In decreasing order of importance, submucosal, intramural, and subserosal UL, have been found to be associated with infertility and pregnancy wastage (Bajekal and Li 2000). A meta-analysis on the association of UL with infertility suggests that only submucosal UL are associated with adverse reproductive outcomes (Pritts 2001), although other studies suggest adverse effects associated with nonsubmucosal UL as well (Rackow and Arici 2005).

Because the location of UL is important, there is a need to identify risk factors not only for the presence of UL in general, but for their specific location, e.g. submucosal versus nonsubmucosal, as well. To date only one epidemiological study has investigated risk factors associated with the location of UL, although results were limited by the small number of women with known location of UL (n = 111) (Faerstein et al. 2001 a). The authors categorized UL as "at least one submucosal" (n=40) and "nonsubmucosal only" (n=71), and used two separate logistic regression models to compare each case subtype group to the group of women without UL (n=394), as additional analyses in the practice-based case-control study. The two logistic regression models were used to evaluate the association of age at first birth and age at first being detected infertile with the location of UL, adjusted for age, clinic, marital status, and ethnicity. Parity was found to be negatively associated with the presence of submucosal UL (versus no UL), and positively associated with the presence of only nonsubmucosal UL (versus no UL). Results for infertility were in the opposite direction.

The odds of having submucosal UL (versus no UL) among women first found to be infertile before age 25 were 7.2 times higher than the same odds among women never found to be infertile, 95% CI: (2.0, 26.0). This was the only statistically significant result found by these additional analyses.

The only statistically significant result was found for the comparison of women first found to be infertile before 25 years old with women never found to be infertile

It should be noted that the main goal of these additional analyses was not to identify risk factors for the location of UL, but rather to argue that infertility and consequent lower parity represent consequences of UL. An alternative hypothesis is that the association of parity with a reduced risk of UL may be due to a protective effect of postpartum involution of the uterus, which may clear small UL during the remodeling of the myometrial tissue (Baird and Dunson 2003). According to this hypothesis, the greatest protective effect of parity would occur for pregnancies during the mid-reproductive years. The Eker rat model for UL supports the latter hypothesis of a protective effect of pregnancy (Walker et al. 2001).

Although there are proven differences between submucosal, intramural, and subserosal UL beyond their anatomic location, only one study to date has considered the location of UL as the outcome for an additional analysis.

Epidemiology of Stress Urinary Incontinence

Urinary incontinence is one of the most common types of lower urinary tract dysfunction, affecting about a third of adult women in the United States (DuBeau 2001). The annual direct cost of urinary incontinence for women in the US is estimated as $12.4 billion (in 1995 dollars) (Wilson et al. 2001).

The most recent report from the Standardization Sub-committee of the International Continence Society (Abrams et al. 2002) proposed uniform definitions of the symptoms, signs, urodynamic observations, and conditions associated with lower urinary tract dysfunction. The symptom of stress urinary incontinence (SUI), one of the lower urinary tract storage symptoms, is defined as the *complaint* of involuntary leakage on effort or exertion, or on sneezing or coughing. The sign of SUI is defined as the *observation* of involuntary leakage from the urethra, synchronous with exertion/effort, or sneezing or coughing. Urodynamic stress incontinence is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction, and it is noted during filling cystometry (the method by which the pressure/volume relationship of the bladder is measured during bladder filling) (Abrams et al. 2002).

The focus of this review will be on SUI symptoms, not on the sign of SUI or urodynamic stress incontinence. SUI is one of the three most common subtypes of urinary incontinence symptoms; the others are urge urinary incontinence (associated with urgency, i.e. the sudden compelling desire to pass urine), and mixed urinary incontinence (associated with urgency, exertion, effort, coughing, or sneezing) (Fine et al. 2004).

According to the literature SUI is the most common type of urinary incontinence in women (Miller 2005), occurring at least weekly in at least a third of adult women (Nygaard and Heit 2004). Nearly half of women with urinary incontinence suffer from SUI (Hampel et al. 1997). About half of all women report symptoms of SUI during pregnancy that in most cases disappear after delivery (Nygaard and Heit 2004). In addition to the pressure effect of the enlarged uterus and changes in renal, bladder and urethral function, the reproductive hormone relaxin may also play a role in SUI during pregnancy (Kristiansson et al. 2001).

A recent population-based postal survey of 6,000 women aged between 30 and 90 years who were enrolled in a health maintenance organization (Group Health Cooperative) found that among women with urinary incontinence the prevalence of self-reported SUI (SUI in the absence of urge urinary incontinence, occurring at least monthly) decreased with age, from 45% for women aged 30 to 39 years old, to 16% for women aged 80 to 90 years old (Melville et al. 2005). The results are in agreement with a previous review that concluded that the proportion of women with SUI (and without urge urinary incontinence) among women with urinary incontinence is highest among younger women (Thom 1998).

There is a higher prevalence of SUI symptoms among Caucasian women than among African-American women. A survey of 2,370 women attending a university gynecologic clinic noted that 39% of the Caucasian women reported SUI, compared with only 27% of African-American women (Sze et al. 2002). Parous Caucasian women between 30 and 50 years of age were significantly more likely to have SUI symptoms than African-American women of similar age and parity (Sze et al. 2002).

The estimated increase in the lifetime medical cost of treating a woman with SUI is $58,000 (in 2002 US dollars) resulting in total lifetime medical costs that are 1.8 times greater than the costs for a demographically similar woman without SUI (Birnbaum et al. 2003). SUI accounts for 85% of treatment expenditures for urinary incontinence for women (Wilson et al. 2001). SUI also has a negative impact on the quality of life; women with SUI may be prevented from participating in sports activities, meeting people or shopping. They may feel less attractive, be less sexually active, and have low self-esteem and more anxiety and depression than other women (Contreras-Ortiz 2004).

Epidemiological studies on SUI differ with respect to outcome definitions, study populations, study designs, and data collection. Table 1.2 includes epidemiological studies on risk factors for SUI that included adjustment for potential confounders. These published studies were found through a careful review of the literature. Recognizing their role as established risk factors for SUI, the majority of the studies adjusted for age, BMI, and parity.

Thirty-two papers investigated risk factors for SUI, including 21 cross-sectional studies, 6 prospective cohort studies, 3 retrospective cohort studies, 2 case-control studies, and one randomized clinical trial. One paper described both a cross-sectional study and a retrospective cohort study (Hojberg et al. 1999). Most of the studies were population-based. Outcome definitions included self-reported symptoms of SUI during the previous year (8), the previous month (4), the prior week (2), 4 years after the first delivery (1), 5 years after first delivery (1), and current (i.e. at the time of data collection) (2). Most of the studies considered the outcome defined as SUI vs. no SUI, regardless of the presence or absence of urge urinary incontinence. The other eleven studies defined the outcome as SUI only (i.e. SUI present, urge urinary incontinence absent) vs. no incontinence (i.e. both SUI and urge urinary incontinence absent). Participants were women from U.S.A. (8), Denmark (7), Norway (5), U.K. (3), France (2), Sweden (2), Italy (1), Taiwan (1), South Korea (1), Thailand (1), and China (1).

Established risk factors for SUI include ethnicity, age, BMI, parity, and mode of delivery. Four studies examined the effect of ethnicity. Caucasian ethnicity (vs. African-American) was associated with SUI during the previous week (Brown et al. 1999), SUI occurring weekly or more during the past year (Jackson et al. 2004), SUI some of the time or more (Handa et al. 2004), and at least weekly SUI during the last year (Thom et al. 2006).

Older age has been associated with current SUI (Peyrat et al. 2002, Goldberg et al. 2003, Goldberg et al. 2005, Song et al. 2005), SUI during the last month (Rohr et al. 2005), SUI during the last week (Schytt et al. 2004), and SUI occurring monthly or more (McGrother et al. 2006). As noted before, all studies included age as a potential confounder, although they may not necessarily report on the association of age with SUI specifically.

BMI was positively associated with the presence of SUI during the previous year (Mommsen and Foldspang 1994, Hojberg et al. 1999), once a week or more SUI (Nygaard 1997), SUI during the previous month (Parazzini et al. 2003, Rohr et al. 2005), SUI during the previous week (Brown et al. 1999), current SUI (Goldberg et al. 2003, Goldberg et al. 2005), SUI occurring weekly or more during the past year (Jackson et al. 2004), and SUI occurring some of the time or more during last month (Handa et al. 2004). Higher BMI was associated with an increased risk of SUI (Kuh et al. 1999), weekly or more SUI (Moller et al. 2000), and SUI occurring monthly or more (McGrother et al. 2006). Obesity was associated with SUI (Hannestad et al. 2003, Song et al. 2005), SUI at least several times a month at 1-year follow-up (Dallosso et al. 2003), sometimes or more SUI (Teleman et al. 2004), and SUI one year after childbirth (Schytt et al. 2004). Obesity was defined as BMI > 40 (Hannestad et al. 2003), BMI > 30 (Dallosso et al. 2003, Teleman et al. 2004, Schytt et al. 2004) or as BMI $> 75^{th}$ percentile (Song et al. 2005). Elevated BMI since age 25 has also been associated with SUI (Teleman et al. 2004).

Parity was associated with SUI during the previous year (Foldspang et al. 1992), current SUI (Nygaard 1997, Rortveit et al. 2001, Peyrat et al. 2002, Chen et al. 2003, Goldberg et al. 2005, Song et al. 2005), SUI during the last month (Rohr et al. 2005, Manonai et al. 2005), weekly or more SUI (Moller et al. 2000), SUI some of the time or more

(Handa et al. 2004), SUI during the last week (Schytt et al. 2004), and SUI occurring monthly or more (McGrother et al. 2006). The effects of parity seem to disappear with older age (Rortveit et al. 2001).

Previous vaginal delivery has been associated with current SUI (Peyrat et al. 2002, Song et al. 2005). Having a history of four or more vaginal deliveries was associated with SUI during the past year (Han et al. 2005). A history of vaginal only deliveries (vs. Cesarean only) was associated with SUI (Rortveit et al. 2003 a). The history of at least one vaginal delivery (vs. Cesarean only) has been associated with SUI (Goldberg et al. 2003, Handa et al. 2004, Goldberg et al. 2005). History of vaginal birth vs. nulliparous was associated with SUI during the last year (Hojberg et al. 1999). History of vaginal birth vs. nulliparous and history of Cesarean section vs. nulliparous were both associated with SUI during the last month (Parazzini et al. 2003). Among primiparous women, Cesarean at first delivery (vs. vaginal delivery) has been associated with a reduced risk of SUI 4 years after the first delivery (Fritel et al. 2004), and one year after the childbirth (Schytt et al. 2004). Among parous women, a history of vaginal delivery vs. Cesarean section was associated with SUI during the last month (Manonai et al. 2005).

Conflicting results have been found regarding associations between SUI and HRT use (Parazzini et al. 2003, Teleman et al. 2004, Hendrix et al. 2005), postmenopausal status (Kuh et al. 1999, Manonai et al. 2005, Goldberg et al. 2005), alcohol consumption (Teleman et al. 2004, Song et al. 2005), and occupation (Han et al. 2005, Manonai et al. 2005, Song et al. 2005).

Risk factors identified by at most two studies include use of diuretics (Moller et al. 2000, Rohr et al. 2005), current oral estrogen use (Jackson et al. 2004), higher waist-to-hip

ratio (Brown et al. 1999), higher waist circumference (Han et al. 2005), higher level of education (Kuh et al. 1999), current cigarette smoking (Hannestad et al. 2003), and low impact physical activity (Hannestad et al. 2003).

Other risk factors for SUI identified by only one study include several types of surgery (Mommsen et al. 1993, Moller et al. 2000, Peyrat et al. 2002, Chen et al. 2003, Song et al. 2005), delivery-related variables (Hojberg et al. 1999, Parazzini et al. 2003, Rortveit et al. 2003 b, Fritel et al. 2004), pregnancy and sports-related incontinence-type variables (Nygaard 1997, Viktrup and Lose 2001, Peyrat et al. 2002, Fritel et al. 2004, Schytt et al. 2004), constipation variables (Schytt et al. 2004, Song et al. 2005, McGrother et al. 2006), health status variables (Kuh et al. 1999, McGrother et al. 2006), history of various medical conditions (Chen et al. 2003, Jackson et al. 2004, Song et al. 2005, Rohr et al. 2005, McGrother et al. 2006), family history of SUI (Hannestad et al. 2004), and diet variables (like bread consumption, carbonated drinks consumption, etc.) (Dallosso et al. 2003, Hannestad et al. 2003).

Uterine Leiomyomata and Stress Urinary Incontinence

Uterine enlargement due to the presence of UL, in particular large subserosal UL located in the anterior lower part of the uterus, is believed to cause urinary symptoms by compressing the urinary bladder, which is located in front of the uterus (Haney 2000). In particular, laughing, coughing, or sneezing, may push UL against the bladder and cause involuntary loss of urine (i.e. SUI). Several papers have stated that UL may be associated with SUI (Stovall 2001, Altman et al. 2003, Nygaard and Heit 2004). There is also a case report of a pedunculated UL causing acute SUI (Isherwood et Rane 1999).

One cross–sectional study involving 1,293 women scheduled for hysterectomy from the Maryland Women's Health Study evaluated the association of UL (as the primary diagnosis for hysterectomy) with self-reported SUI during the previous month (Handa et al. 2004). Women with UL as a primary diagnosis were as likely to report SUI as women who had other primary diagnoses, such as noninfectious conditions, cancer and premalignant conditions, adnexal conditions, and infections. It should be noted that the study did not compare the prevalence of SUI among women with UL to women without UL, and that the study was not population-based.

The association between UL and urinary incontinence (not SUI) has been investigated in only one study to date (Sampselle et al. 2002). This study used baseline data from the longitudinal cohort of the Study of Women's Health Across the Nation, a multiethnic study of the natural history of menopausal transition. Participants were 3,302 women aged 42 to 52 years old, 47% of whom were Caucasian, 28% African-American, and the rest Chinese, Hispanic, and Japanese. Women were classified as having UL if they reported that a health care provider had ever told them that they had the condition. Among women without a history of UL, African-American women were less likely than Caucasian women to report urinary incontinence, OR = 0.31, 95% CI: (0.23, 0.40). However, among women with history of UL, African-American women were more likely than Caucasian women to report urinary incontinence, OR = 1.81, 95% CI: (1.22, 2.71). The authors did not report race-specific odds ratios for the association of history of UL with urinary incontinence. Results were adjusted for age, menopausal status, BMI, diabetes, and parity. To explain the finding the authors speculated that the propensity of African-American women to develop larger UL resulted in

an increased prevalence of SUI, and subsequently an increased prevalence of urinary incontinence.

Research on changes in SUI symptoms before and after hysterectomy (or other treatments) may provide indirect information about the association between UL and SUI. In a small study including 14 patients with large UL treated with monthly injections of gonadotropin-releasing hormone analogues, the number of patients with SUI decreased from 6 to 5. Based on this, the authors concluded that SUI is probably unrelated to uterine size; however the small numbers involved prevent any meaningful conclusion regarding the association of UL with SUI based on this study (Langer et al. 1990).

A randomized double blind clinical trial, comparing urinary function outcomes after total and subtotal abdominal hysterectomy, found reductions in SUI symptoms in both treatment groups, and the reductions were similar in the two groups (Thakar et al. 2002). The authors stated that improvements in SUI symptoms were not associated with the presence or absence of UL, without providing any data to support their claim, and further concluded that improvements could not be attributed to the elimination of the pressure effects of the UL.

In a prospective observational study designed to compare the effects of different hysterectomy techniques (total abdominal, vaginal, laparoscopic, and subtotal) on urinary and sexual function, patients reported significantly lower rates of SUI six months after surgery than before the operation, regardless of the technique used (El-Toukhy et al. 2004). The primary indications for hysterectomy were abnormal uterine bleeding (43%) and UL (41%). The prevalence of SUI dropped from 36% before the surgery to 19% 6 months after the surgery ($p=0.005$). It was also stated that the presence of UL before surgery was associated with improvement in urinary symptoms after hysterectomy, without specific

reference to improvement of SUI symptoms. The authors attributed the improvement in some of the urinary symptoms to postoperative urethral obstruction and bladder neck elevation associated with hysterectomy.

A Danish multicenter randomized controlled trial, investigating lower urinary tract symptoms after total and subtotal hysterectomy, found a decreased number of patients reporting SUI after surgery (Gimbel et al. 2005). In the total hysterectomy group the prevalence decreased from 9% to 2% one year later. In the subtotal hysterectomy group the decrease was smaller, from 9% to 6% one year later. The reduction of SUI in both groups was attributed to the removal of uteri with large UL; the larger reduction in the total hysterectomy group was attributed to the minor bladder neck suspension associated with the procedure.

REFERENCES

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van KP, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol. 2002 Jul;187:116-126.

Altman D, Lopez A, Falconer C, Zetterstrom J. The impact of hysterectomy on lower urinary tract symptoms. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Dec;14:418-423.

Baird DD, Kesner JS, Dunson DB. Luteinizing hormone in premenopausal women may stimulate uterine leiomyomata development. J Soc Gynecol Investig. 2006 Feb;13:130-135.

Baird DD. Invited commentary: uterine leiomyomata-we know so little but could learn so much. Am J Epidemiol. 2004 Jan 15;159:124-126.

Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology. 2003 Mar;14:247-250.

Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. Reprod Toxicol. 2005 May-Jun;20:81-84.

Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. Association of physical activity with development of uterine leiomyoma. Am J Epidemiol. 2007 Jan 15;165:157-163.

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 Jan;188:100-107.

Bajekal N, Li TC. Fibroids, infertility and pregnancy wastage. Hum Reprod Update. 2000 Nov-Dec;6:614-620.

Birnbaum H, Leong S, Kabra A. Lifetime medical costs for women: cardiovascular disease, diabetes, and stress urinary incontinence. Womens Health Issues. 2003 Nov-Dec;13:204-213.

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 Apr 1;161:628-638.

Brett KM, Marsh JV, Madans JH. Epidemiology of hysterectomy in the United States: demographic and reproductive factors in a nationally representative sample. J Womens Health. 1997;6:309-316.

Brosens I, Deprest J, Dal CP, Van dH: Clinical significance of cytogenetic abnormalities in

uterine myomas. Fertil Steril. 1998; 69:232-235

Brosens J, Campo R, Gordts S, Brosens I: Submucous and outer myometrium leiomyomas are two distinct clinical entities. Fertil Steril. 2003 Jun;79:1452-1454

Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: a systematic review. Lancet. 2000 Aug 12;356:535-539.

Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol. 1999; 94:66-70.

Chen CR, Buck GM, Courey NG, Perez KM, Wactawski-Wende J. Risk factors for uterine fibroids among women undergoing tubal sterilization. Am J Epidemiol. 2001 Jan 1;153:20-26.

Chen GD, Lin TL, Hu SW, Chen YC, Lin LY. Prevalence and correlation of urinary incontinence and overactive bladder in Taiwanese women. Neurourol Urodyn. 2003;22:109-117.

Chiaffarino F, Parazzini F, La VC, Chatenoud L, Di CE, Marsico S. Diet and uterine myomas. Obstet Gynecol. 1999; 94:395-398.

Chiaffarino F, Parazzini F, La VC, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol. 1999;106:857-860.

Contreras OO. Stress urinary incontinence in the gynecological practice. Int J Gynaecol Obstet. 2004 Jul;86 Suppl 1:S6-16.

Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990;94:435-438.

D'Aloisio AA, Baird DD. Variation in the association of alcohol intake with uterine fibroids by race and tumor size. Ann Epid. 2004;14:622-622.

Dallosso HM, McGrother CW, Matthews RJ, Donaldson MM. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU Int. 2003 Jul;92:69-77.

DuBeau CE. Urinary incontinence management: new questions from old assumptions. J Am Geriatr Soc. 2001; Jun 49:829-830.

El-Toukhy TA, Hefni M, Davies A, Mahadevan S. The effect of different types of hysterectomy on urinary and sexual functions: a prospective study. J Obstet Gynaecol. 2004 Jun;24:420-425.

Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril. 1998; 70:687-691.

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 Jan 1;153:11-19.

Faerstein E, Szklo M, Rosenshein N. Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage, reproductive history, body size, and smoking. Am J Epidemiol. 2001 Jan 1;153:1-10.

Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol. 2002 Feb; 99:229-234.

Fine PM, Antonini TG, Appell RA. Clinical evaluation of women with lower urinary tract dysfunction. Clin Obstet Gynecol. 2004; Mar;47:44-52.

Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003 Jun;111:1037-1054.

Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol. 2006 Oct;195:955-964.

Foldspang A, Mommsen S, Lam GW, Elving L. Parity as a correlate of adult female urinary incontinence prevalence. J Epidemiol Community Health. 1992; 46:595-600.

Fritel X, Fauconnier A, Levet C, Benifla JL. Stress urinary incontinence 4 years after the first delivery: a retrospective cohort survey. Acta Obstet Gynecol Scand. 2004 Oct;83:941-945.

Gimbel H, Zobbe V, Andersen BJ, Sorensen HC, Toftager-Larsen K, Sidenius K, Moller N, Madsen EM, Vejtorp M, Clausen H, Rosgaard A, Villumsen J, Gluud C, Ottesen BS, Tabor A. Lower urinary tract symptoms after total and subtotal hysterectomy: results of a randomized controlled trial. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Jul-Aug;16:257-262.

Goldberg RP, Abramov Y, Botros S, Miller JJ, Gandhi S, Nickolov A, Sherman W, Sand PK. Delivery mode is a major environmental determinant of stress urinary incontinence: results of the Evanston-Northwestern Twin Sisters Study. Am J Obstet Gynecol. 2005 Dec;193:2149-2153.

Goldberg RP, Kwon C, Gandhi S, Atkuru LV, Sand PK. Urinary incontinence after multiple gestation and delivery: impact on quality of life. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Sep-Oct;16:334-336.

Goldberg RP, Kwon C, Gandhi S, Atkuru LV, Sorensen M, Sand PK. Urinary incontinence among mothers of multiples: the protective effect of cesarean delivery. Am J Obstet Gynecol. 2003 Jun;188:1447-1450.

Hampel C, Wienhold D, Benken N, Eggersmann C, Thuroff JW. Definition of overactive bladder and epidemiology of urinary incontinence. Urology. 1997; 50:4-14discussion.

Hampel C, Wienhold D, Benken N, Eggersmann C, Thuroff JW. Prevalence and natural history of female incontinence. Eur Urol. 1997; 32 Suppl 2:3-12.

Han MO, Lee NY, Park HS. Abdominal obesity is associated with stress urinary incontinence in Korean women. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jan;17:35-39.

Handa VL, Harvey L, Fox HE, Kjerulff KH. Parity and route of delivery: does cesarean delivery reduce bladder symptoms later in life? Am J Obstet Gynecol. 2004 Aug;191:463-469.

Haney AF. Clinical decision making regarding leiomyomata: what we need in the next millenium. Environ Health Perspect. 2000 Oct;108 Suppl 5:835-839.

Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. BMJ. 2004 Oct 16;329:889-891.

Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG. 2003 Mar;110:247-254.

Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, Aragaki A, Naughton MJ, Wallace RB, McNeeley SG. Effects of estrogen with and without progestin on urinary incontinence. JAMA. 2005 Feb 23;293:935-948.

Hojberg KE, Salvig JD, Winslow NA, Lose G, Secher NJ. Urinary incontinence: prevalence and risk factors at 16 weeks of gestation. Br J Obstet Gynaecol. 1999;106:842-850.

Isherwood PJ, Rane A. Pedunculated uterine leiomyoma causing acute urinary stress incontinence. J Obstet Gynaecol. 1999;19:440-441.

Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, Simonsick EM, Brown JS. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol. 2004 Aug;104:301-307.

Keshavarz H, Hillis S, Kieke B, and Marchbanks P. Hysterectomy Surveillance --- United States, 1994--1999. 51(SS05); 1-8. 7-12-2002. CDC Surveillance Summaries.

Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med.

1996;41:483-490.

Kristiansson P, Samuelsson E, von SB, Svardsudd K. Reproductive hormones and stress urinary incontinence in pregnancy. Acta Obstet Gynecol Scand. 2001 Dec;80:1125-1130.

Kuh D, Cardozo L, Hardy R. Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. J Epidemiol Community Health. 1999;53:453-458.

Langer R, Golan A, Neuman M, Schneider D, Bukovsky I, Caspi E. The effect of large uterine fibroids on urinary bladder function and symptoms. Am J Obstet Gynecol. 1990;163:1139-1141.

Lumbiganon P, Rugpao S, Phandhu-fung S, Laopaiboon M, Vudhikamraksa N, Werawatakul Y. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case--control study. Br J Obstet Gynaecol. 1996;103:909-914.

Manonai J, Poowapirom A, Kittipiboon S, Patrachai S, Udomsubpayakul U, Chittacharoen A. Female urinary incontinence: a cross-sectional study from a Thai rural area. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Sep 24;1-5.

Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, Stampfer MJ, Hunter DJ. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril. 1998;70:432-439.

Marshall LM, Spiegelman D, Manson JE, Goldman MB, Barbieri RL, Stampfer MJ, Willett WC, Hunter DJ. Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. Epidemiology. 1998;9:511-517.

Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol. 1997;90:967-973.

McGrother CW, Donaldson MM, Hayward T, Matthews R, Dallosso HM, Hyde C. Urinary storage symptoms and comorbidities: a prospective population cohort study in middle-aged and older women. Age Ageing. 2006 Jan;35:16-24.

Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med. 2005 Mar 14;165:537-542.

Miller KL. Stress urinary incontinence in women: review and update on neurological control. J Womens Health (Larchmt). 2005 Sep;14:595-608.

Moller LA, Lose G, Jorgensen T. The prevalence and bothersomeness of lower urinary tract

symptoms in women 40-60 years of age. Acta Obstet Gynecol Scand. 2000; Apr;79:298-305.

Mommsen S, Foldspang A. Body mass index and adult female urinary incontinence. World J Urol. 1994;12:319-322.

Mommsen S, Foldspang A, Elving L, Lam GW. Association between urinary incontinence in women and a previous history of surgery. Br J Urol. 1993;72:30-37.

Nygaard IE, Heit M. Stress urinary incontinence. Obstet Gynecol. 2004 Sep;104:607-620.

Nygaard IE. Does prolonged high-impact activity contribute to later urinary incontinence? A retrospective cohort study of female Olympians. Obstet Gynecol. 1997; 90:718-722.

Parazzini F, Chiaffarino F, Polverino G, Chiantera V, Surace M, La VC. Uterine fibroids risk and history of selected medical conditions linked with female hormones. Eur J Epidemiol. 2004;19:249-253.

Parazzini F, Chiaffarino F, Lavezzari M, Giambanco V. Risk factors for stress, urge or mixed urinary incontinence in Italy. BJOG. 2003 Oct;110:927-933.

Parazzini F, Negri E, La VC, Chatenoud L, Ricci E, Guarnerio P. Reproductive factors and risk of uterine fibroids. Epidemiology. 1996; 7:440-442.

Parazzini F, Negri E, La VC, Rabaiotti M, Luchini L, Villa A, Fedele L. Uterine myomas and smoking. Results from an Italian study. J Reprod Med. 1996; 41:316-320.

Parazzini F, La VC, Negri E, Cecchetti G, Fedele L. Epidemiologic characteristics of women with uterine fibroids: a case-control study. Obstet Gynecol. 1988; 72:853-857.

Parazzini F, Negri E, La VC, Fedele L, Rabaiotti M, Luchini L. Oral contraceptive use and risk of uterine fibroids. Obstet Gynecol. 1992; 79:430-433.

Peyrat L, Haillot O, Bruyere F, Boutin JM, Bertrand P, Lanson Y. Prevalence and risk factors of urinary incontinence in young and middle-aged women. BJU Int. 2002 Jan;89:61-66.

Pritts EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv. 2001 Aug;56:483-491.

Rackow BW, Arici A. Fibroids and in-vitro fertilization: which comes first? Curr Opin Obstet Gynecol. 2005 Jun;17:225-231.

Ramcharan, S., Pellegrin, F. A., Ray, R. M., and Hsu, J. P. The Walnut Creek Contraceptive Drug Study. A prospective study of the side effects of oral contraceptives. (3), 69-74. 12-1981. Center Popul Res Monogr.

Reed SD, Cushing-Haugen KL, Daling JR, Scholes D, Schwartz SM. Postmenopausal estrogen and progestogen therapy and the risk of uterine leiomyomas. Menopause. 2004 Mar-Apr;11:214-222.

Robboy SJ, Bentley RC, Butnor K, Anderson MC. Pathology and pathophysiology of uterine smooth-muscle tumors. Environ Health Perspect. 2000 Oct;108 Suppl 5:779-784.

Rohr G, Stovring H, Christensen K, Gaist D, Nybo H, Kragstrup J. Characteristics of middle-aged and elderly women with urinary incontinence. Scand J Prim Health Care. 2005 Dec;23:203-208.

Romieu I., Walker AM, and Jick S. Determinants of uterine fibroids. Post Market Surveil 1991 5: 119-133

Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S. Vaginal delivery parameters and urinary incontinence: the Norwegian EPINCONT study. Am J Obstet Gynecol. 2003 Nov;189:1268-1274.

Rortveit G, Daltveit AK, Hannestad YS, Hunskaar S. Urinary incontinence after vaginal delivery or cesarean section. N Engl J Med. 2003 Mar 6;348:900-907.

Rortveit G, Hannestad YS, Daltveit AK, Hunskaar S. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. Obstet Gynecol. 2001 Dec;98:1004-1010.

Rosati P, Bellati U, Exacoustos C, Angelozzi P, Mancuso S. Uterine myoma in pregnancy: ultrasound study. Int J Gynaecol Obstet. 1989; 28:109-117.

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; 293:359-362.

Samadi AR, Lee NC, Flanders WD, Boring JR, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. Am J Public Health. 1996; 86:858-862.

Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol. 2002 Dec;100:1230-1238.

Sato F, Nishi M, Kudo R, Miyake H. Body fat distribution and uterine leiomyomas. J Epidemiol. 1998; 8:176-180.

Schwartz SM. Epidemiology of uterine leiomyomata. Clin Obstet Gynecol. 2001 Jun;44:316-326.

Schwartz SM. Invited commentary: Studying the epidemiology of uterine leiomyomata--past,

present, and future. Am J Epidemiol. 2001 Jan 1;153:27-29.

Schytt E, Lindmark G, Waldenstrom U. Symptoms of stress incontinence 1 year after childbirth: prevalence and predictors in a national Swedish sample. Acta Obstet Gynecol Scand. 2004 Oct;83:928-936.

Song YF, Zhang WJ, Song J, Xu B. Prevalence and risk factors of urinary incontinence in Fuzhou Chinese women. Chin Med J (Engl). 2005 Jun 5;118:887-892.

Stewart EA. Uterine fibroids. Lancet. 2001 Jan 27;357:293-298.

Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol. 2001 Jun;44:364-371.

Sze EH, Jones WP, Ferguson JL, Barker CD, Dolezal JM. Prevalence of urinary incontinence symptoms among black, white, and Hispanic women. Obstet Gynecol. 2002 Apr;99:572-575.

Teleman PM, Lidfeldt J, Nerbrand C, Samsioe G, Mattiasson A. Overactive bladder: prevalence, risk factors and relation to stress incontinence in middle-aged women. BJOG. 2004 Jun;111:600-604.

Thakar R, Ayers S, Clarkson P, Stanton S, Manyonda I. Outcomes after total versus subtotal abdominal hysterectomy. N Engl J Med. 2002 Oct 24;347:1318-1325.

Thom DH. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. J Am Geriatr Soc. 1998; 46:473-480.

Thom DH, van dK, Ragins AI, Wassel-Fyr C, Vittinghof E, Subak LL, Brown JS. Differences in prevalence of urinary incontinence by race/ethnicity. J Urol. 2006 Jan;175:259-264.

Thom DH, Brown JS. Reproductive and hormonal risk factors for urinary incontinence in later life: a review of the clinical and epidemiologic literature. J Am Geriatr Soc. 1998; 46:1411-1417.

Van Voorhis BJ, Romitti PA, Jones MP. Family history as a risk factor for development of uterine leiomyomas. Results of a pilot study. J Reprod Med. 2002 Aug;47:663-669.

Velebil P, Wingo PA, Xia Z, Wilcox LS, Peterson HB. Rate of hospitalization for gynecologic disorders among reproductive-age women in the United States. Obstet Gynecol. 1995;86:764-769.

Viktrup L, Lose G. The risk of stress incontinence 5 years after first delivery. Am J Obstet Gynecol. 2001 Jul;185:82-87.

Viktrup L, Lose G. Lower urinary tract symptoms in fertile women after pregnancy and labor. Ugeskr Laeger. 2001;2001 Sep 17;163:5180-5182.

Walker CL, Stewart EA. Uterine fibroids: the elephant in the room. Science. 2005 Jun 10;308:1589-1592.

Walker CL, Cesen-Cummings K, Houle C, Baird D, Barrett JC, Davis B. Protective effect of pregnancy for development of uterine leiomyoma. Carcinogenesis. 2001 Dec;22:2049-2052.

Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. Obstet Gynecol. 2001 Sep;98:398-406.

Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, Rosenberg L. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology. 2005 May;16:346-354.

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 Mar;105:563-568.

Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Hum Reprod. 2004 Aug;19:1746-1754.

Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol. 2004 Jan 15;159:113-123.

TABLE 1.1. Epidemiological papers that have investigated risk factors for uterine leiomyomata.

Study (year)	Population Design Sample size	Outcome Definition	Risk Factors Examined	Adjusted for	Results
The Royal College of General Practitioners (1974)	The Oral Contraception Study of the RCGP Prospective 23,611 Takers 22,766 controls matched by age and marital status At least 15 years old	Diagnostic based on the resources of the National Health Service and the assessment of the general practitioner (ICD 8 code 218)	Use of oral contraceptives	Indirect standardization using age, parity, social class, and cigarette consumption	Ratio of standardized rates: Takers vs. controls: 0.41 ($p<0.01$)
Ramcharan et al. (1981)	The Walnut Creek Contraceptive Drug Study Prospective 14,591 women 18 to 54 years of age Mainly Caucasian	Based on hospital discharge diagnoses and operative procedures coded with ICDA-8 (UL ICDA 218)	Use of oral contraceptives	Indirect standardization using age, parity, education, smoking, and estrogen use	RR (relative risk) Ever users vs. never users: 1.5 (1.9-2.7)
Ross et al. (1986)	UK Case-control study 535 cases	Pathologically confirmed	Term pregnancies, age at first term pregnancy, age at last term pregnancy, menopausal status, time	Matching by age, date of entry into the cohort, and family planning	Each term birth: 0.80 5 years increase in age at last term

	535 controls Oxford Family Planning Association Study		since last use of OC, duration of use of OC up to 6 months before diagnosis, weight, BMI, number of cigarettes per day	clinic at recruitment Mutual adjustment	birth: 0.78 Postmenopausal: 0.18 5 years use of OC: 0.83 10 kg increase in weight: 1.21 10 cigarettes/day: 0.82
Parazzini et al. (1988)	Italy Hospital-based case-control 275 cases 722 controls	Histologically confirmed (after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm)	Age, parity/age at last birth, age at menarche, menopausal status, IUD use, education, smoking, BMI	Mutually adjusted for the risk factors of interest	Parity 3+ vs. 0: 0.5 (0.3-0.9) Post vs. pre: 0.1 (0.05-0.2) 15+ cig/d vs. never: 0.5 (0.3-0.8)
Romieu et al. (1991)	Population-based case-control study 345 cases 749 controls Group Health Cooperative	Primary hospital discharge diagnosis after hysterectomy	Age at menarche, age at first birth, OC use and duration, estrogen use and duration, cigarette smoking, menopausal status, BMI	Age, duration of OC use, duration of estrogen use, menopausal status, smoking status	[Age-adjusted] Prior use of replacement estrogen: 1.9 (1.5-2.5) Onset of menopause: 0.07 (0.04-0.14) Ever smoked: 0.65 (0.48-0.88)
Parazzini et al. (1992)	Italy Hospital-based case-control 390 cases 1,136 controls	Histologically confirmed (after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm)	OC use, duration of use, time since last use, time since first use	Age, education, marital status, parity, nr of spontaneous abortions, nr of induced abortions,	No statistically significant results Example: Ever OC use vs. never 1.1 (0.8-1.5)

				menopausal status	
Lumbiganon et al. (1996)	Thailand Hospital-based case-control 910 cases 2709 controls	Pathologically confirmed	Use of depot-medroxyprogesterone acetate (DMPA), duration of use, time since last dose, oral contraceptives use, IUCD use, tubal ligation, age at menarche, age at first delivery, age at last delivery, parity, number of abortions, breast-feeding, age at first marriage, marital status, race, education, occupation, smoking, BMI, OC use, tubal ligation, family history of UL	Mutual adjustment	Ever DMPA use vs. never: 0.42 (0.34-0.53) DMPA >5 years vs. never: 0.11 (0.05-0.23) DMPA >10 years since last dose vs. never: 0.66 (0.50-0.86) Ever OC use vs. never: 0.76 (0.66-0.92) Tubal ligation: 1.67 (1.42-1.97) Family history of UL: 3.47 (2.55-4.71) Parity: 0.77 (0.72-0.82) Education (years): 1.03 (1.02-1.06) BMI (kg/m^2): 1.06 (1.04-1.08) Smoking: 0.63 (0.40-0.99) Abortions 3+ vs. none: 1.94 (1.18-3.19)

Samadi et al. (1996)	Case-control 201 cases 1,503 controls Aged 20 to 54 years old Cancer and Steroid Hormone Study	Self-report of a physician diagnosis of UL	Menopausal status, OC use, frequency of Pap smears, education, BMI, smoking	Age at index date, race, age at menarche, duration of breast-feeding	Premenopausal vs. postmenopausal: 3.5 (1.7-7.2) OC use 3+ months vs. < 3 months, among those with < 1 Pap smear per 5 years: 5.0 (1.1-24.0) Current smokers vs. never smokers among those with low BMI: 0.3 (0.2-0.5)
Parazzini et al. (1995)	Italy Hospital-based case-control 476 cases 1,283 controls	Histologically confirmed after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm	Smoking status, number of cigarettes smoked per day, duration of smoking	Age, education, parity, BMI, and oral contraceptive use	Smoking current vs. never: 0.5 (0.4-0.7)
Parazzini et al. (1996)	Italy Hospital-based case-control 621 cases 1,051 controls Age 21 to 54 years old	Histologically confirmed after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm	Reproductive factors: parity, history of spontaneous abortions, history of induced abortions, age at first birth, age at last birth, history of infertility	Age, education, menopausal status, BMI, oral contraceptive use, and each reproductive factor singly	4+ vs. nulliparous: 0.3 (0.2-0.5) 2+ induced abortions vs. none: 0.6 (0.4-0.9) Infertility history: 2.0 (1.1-3.7)
Marshal et al. (1997)	Premenopausal nurses Prospective cohort	Self-reported confirmed by ultrasound or hysterectomy	Race	Age, time period, marital status, BMI, age at first birth, years since last	RR (relative risk) African-American vs. Caucasian 3.25 (2.71-3.88)

	94,095 The Nurses' Health Study			birth, history of infertility, age at first OC use, current alcohol consumption	
Brett et al. (1997)	NHANES I Epidemiologic Follow-up Study 4665 women 25-49 years old	Hysterectomy due to UL Hospital discharge diagnosis after hysterectomy; ICD-9 codes 218, 654.1	Age at baseline, educational attainment, race, age at first birth, number of pregnancies, number of miscarriages	Mutual adjustment	African-American vs. Caucasian: 1.9 (1.3-2.9)
Sato et al. (1998)	Case-control study 100 cases 200 controls Sapporo City, Japan Premenopausal Aged 29 to 54 years	Pathologically diagnosed cases, controls were confirmed not to have UL by clinical examination	BMI, percent body fat, obesity type, waist-to-hip ratio	No adjustment	Percent body fat 35+ vs. <25: 3.22 (1.34-7.74) Waist-to-hip ratio 0.85+ vs. <0.75: 12.80 (4.50-36.37)
Marshal et al. (1998) a	Prospective cohort 94,095 premenopausal women Aged 25 to 42 years old The Nurses' Health Study	Self-reported confirmed by ultrasound or hysterectomy	Body size (BMI, BMI at age 18, weight gain since age 18, height) and cigarette smoking	Age, race, marital status, age at menarche, age at first birth, years since last birth, history of infertility, age at first OC use	RR (relative risk) Current BMI 30+ vs. 20.0-21.9: 1.23 (1.09-1.39) Weight gain since age 18 of 15 kg or more vs. stable weight (±3.0 kg): 1.48 (1.31-1.66)

Marshall et al. (1998) b	Prospective cohort 95,061 premenopausal women aged 25 to 42 years old The Nurses' Health Study	Self-reported confirmed by ultrasound or hysterectomy	Reproductive factors (age at menarche, parity, age at first birth, years since last birth, history of infertility) and OC use	Age, race, marital status, BMI, and mutually adjusted for the risk factors of interest	RR (relative risk) Age at menarche 16+ vs. 12: 0.68 (0.53-0.88) Parous vs. nulliparous: 0.67 (0.61-0.74) Infertility: 1.28 (1.17-1.41) First used OC when 13-16 years old vs. never: 1.26 (1.05-1.51)
Chiaffarino et al. (1999) a	Italy Case-control 843 cases 1557 controls Aged 21 to 54 years old	Histologically confirmed after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm	Average weekly frequency of consumption of: milk, beef and other red meat, liver, carrots, green vegetables, fresh fruit, eggs, ham, fish, cheese, whole-grain foods, butter, margarine, oil, coffee, tea; total alcohol intake	Age, education, marital status, menopausal status, parity, BMI, smoking, calendar year at interview	Intake increase of one serving per day: Beef and other red meat: 1.8 (1.3-2.4) Ham: 1.9 (1.3-2.90 Green vegetables: 0.6 (0.5-0.8)
Chiaffarino et al. (1999) b	Italy Case-control 843 cases 1557 controls Aged 21 to 54 years old	Histologically confirmed after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm	Oral contraceptive use, duration of use, time since last use, time since first use	Age, calendar year at interview, education, marital status, menopausal status, parity, BMI, miscarriages, and smoking habits	Current OC users vs. never users: 0.3 (0.2-0.6) Ever users for 7 years or more vs. never users: 0.5 (0.3-0.9)

Faerstein et al. (2001) a	Premenopausal women Practice-based case-control 318 cases 394 controls (frequency matched)	Surgically or sonographically confirmed	Age, marital status, ethnicity, education, frequency of gynecologic visits per year, family history, menstrual history, pregnancy and infertility history, BMI, oral contraceptive use, smoking	Adjustment variables varied and included age, ethnicity, clinic, education, marital status, family history, and menstrual history variables	African-American vs. Caucasian: 9.4 (5.7-15.7) Age at menarche 8-10 vs. 14-17: 2.4 (1.1-5.6) Less than 25 years old when found to be infertile vs. never infertile: 2.4 (1.1-5.3) Current OC use vs. never use: 0.2 (0.1-0.6) BMI upper quartile vs. lower quartile: 2.3 (1.4-3.8) Smoked 19+ years vs. never smoker: 0.6 (0.4-1.1)
Faerstein et al. (2001) b	Premenopausal women Practice-based case-control 318 cases 394 controls (frequency matched)	Surgically or sonographically confirmed	Hypertension history, diabetes history, history of pelvic inflammatory disease, history of several sexually transmitted diseases, abnormal Pap smear, use of intrauterine devices, use of perineal talc	Adjustment variables included age, clinic, ethnicity, and BMI	Antihypertensive medication prescribed; 2.1 (1.1-4.1) Antihypertensive medication prescribed of 5 years or more: 3.1 (1.2-8.2) Intrauterine device use when it caused

					infectious complications: 5.3 (1.8-16.3) Use of perineal talc Daily vs. never use: 2.2 (1.4-3.1)
Chen et al. (2001)	Nested case-control design 317 cases 1,268 controls Mostly Caucasian Women undergoing tubal sterilization	Laparoscopic evidence or self-reported history of UL (at the time of tubal sterilization)	Demographics (age, race, education, number of living children), menstrual cycle characteristics (length, regularity, flow, pain, and spotting between cycles), reproductive characteristics (time since last delivery, type of contraception used) and lifestyle characteristics (cigarette smoking, BMI)	Mutual adjustment	Caucasian women Age 40-44 vs. <30: 6.3 (3.5-11.6) 6+ days menstrual bleeding vs. 1-5: 1.4 (1.0-2.0) >30 days menstrual cycle length vs. <=30: 1.6 (1.1-3.3) 2+ living children vs. none (proxy for parity): 0.2 (0.1-0.3) 5+ years since last delivery vs. <1 year: 1.9 (1.1-3.1) 1+ pack/day vs. never smoker: 1.6 (1.1-2.3) African-American

					women Age 40-44 vs. <30: 27.5 (5.6-83.6)
Van Voorhis et al. (2002)	Hospital-based case-control Most Caucasian 81 cases 103 controls Aged 50 or less	Cases: pathologically confirmed Controls: pathologic examination or transvaginal ultrasonography	Family history of UL	Parity and age	Maternal history: 2.85 (1.25-6.52) Parity: 0.75 (0.57-0.98)
Reed et al. (2004)	Peri- and postmenopausal Case-control 256 cases 276 controls Aged 40 to 59 years old Mostly Caucasian	Confirmed by surgery or ultrasound	Use of estrogen and progestogen therapy (EPT)	Age at reference, reference year, menopausal status, and race	Among those with BMI < 24 kg/m^2 Ever EPT vs. never or < 3 months: 2.3 (1.2-4.3) 5+ years of use vs. never or < 3 months: 4.0 (1.6-10.3)
Wise et al. (2004) a	Premenopausal African-American Prospective cohort 22,895 women Black Women's Health Study Age 21 to 69 years old	Self-reported confirmed by ultrasound or hysterectomy	Reproductive characteristics (age at menarche, parity, age at first birth, years since last birth, duration of lactation, history of infertility, number of spontaneous abortions, number of induced abortions), hormonal contraceptive use (current use, years of use, years since last OC	Age, time period, age at menarche, parity, months of lactation, age at first birth, years since last birth, BMI, years of OC use, smoking, and current alcohol consumption	IRR (incidence RR) Age at menarche 15+ vs. <11: 0.7 (0.5-0.8) Parity: 0.7 (0.6-0.8) Age at first birth 30+ vs. <20: 0.6 (0.4-0.9) Years since last birth 20+ vs. <5:

			use, age at first OC use, estrogenic potency, progestational potency, classification of progestin, estrogen formulation)		2.2 (1.4-3.2) Current use of OC Progestin-only injectables vs. none: 0.6 (0.4-0.9)
Wise et al. (2004) b	Premenopausal African-American Prospective cohort 21,885 women Black Women's Health Study Age 21 to 69 years old	Self-reported confirmed by ultrasound or hysterectomy	Various measures of tobacco, alcohol and caffeine consumption	Age, time period, age at menarche, parity, age at first birth, years since last birth, OC use, education, BMI, and mutually adjusted for smoking, alcohol, and caffeine	IRR (incidence RR) Beer, drinks per week, 7+ vs. none: 1.57 (1.17-2.11) Among women <35 years old: Coffee 3+ cups/day vs. almost never: 1.53 (1.06-2.22) Caffeine 500+ vs. <50 mg/day: 1.70 (1.23-2.36)
Parazzini et al. (2004)	Italy Case-control 843 cases 1557 controls age 21 to 54 years old	Histologically confirmed after surgery due to recurrent menorrhagia or echographic evidence of UL > 10 cm	Selected medical conditions such as diabetes, thyroid disease, severe overweight, hypertension, cholelithiasis, hyperlipidaemia, ovarian cysts/benign tumors, benign breast disease, previous breast biopsies	Age, education, parity, cigarette smoking, and calendar year at interview	Clinical history of severe overweight: 0.6 (0.5-0.8) History of breast biopsies: 2.0 (1.2-3.5)

Wise et al. (2005)	Premenopausal African-American Prospective cohort 21,506 women Black Women's Health Study Age 21 to 69 years old	Self-reported confirmed by ultrasound or hysterectomy	Current BMI, BMI at age 18, weight gain since age 18, height, waist, hip, waist-to-hip ratio	Age, time period, age at menarche, parity, age at first birth, years since last birth, OC use, education, smoking, current alcohol consumption, geographic region	Inverse J-shaped relation for BMI IRR (incidence RR) Among parous BMI 27.5-29.9 vs. <20.0: 1.81 (1.15-2.86) Weight gain since age 18, 25+ vs. <5: 1.54 (1.21-1.98) Among nulliparous BMI 22.5-24.9 vs. <20.0: 1.46 (1.04-2.03)
Boynton-Jarrett et al. (2005)	Prospective cohort 104,233 premenopausal women Aged 25 to 42 years old The Nurses' Health Study	Self-reported confirmed by ultrasound or hysterectomy	Diastolic blood pressure, years since diagnosis of hypertension	Age, calendar time, BMI, age at menarche, age at first oral contraceptive use, time since last birth, age at first birth, marital status, ethnicity, menstrual cycle length and regularity, and history of infertility	RR Nonusers of antihypertensive medications: Diastolic blood pressure increase of 10 mmHg: 1.08 (1.05-1.11) Users of antihypertensive medications: Diastolic blood pressure increase of 10 mmHg: 1.10 (1.07-1.13)

Baird and Newbold (2005)	Cross-sectional 819 African-American 504 Caucasian Aged 35 to 49 years old NIEHS Uterine Fibroid Study	Ultrasound, surgical record review, self-report of prior diagnosis	Prenatal diethylstilbestrol (DES) exposure	Age, age at menarche, BMI, exercise, family history of UL, and number of full term pregnancies delivered at age 25 or older	Caucasian women 2.4 (1.1-5.4) [Adjusted for age]
Baird et al. (2006)	Cross-sectional 523 women postmenopausal Aged 35 to 49 years old NIEHS Uterine Fibroid Study	Ultrasound, surgical record review, self-report of prior diagnosis	Luteinizing hormone levels	Age, ethnicity, age at menarche, BMI, number of full-term pregnancies after age 24, and exercise	Tertiles 2^{nd} vs. 1^{st}: 1.7 (1.0-2.7) Tertiles 3^{rd} vs. 1^{st}: 2.0 (1.2-3.4) Age (5 years): 1.7 (1.3-2.1)

TABLE 1.2. Epidemiological papers that have investigated risk factors for stress urinary incontinence (SUI).

Study (year)	Population Design Sample size	Outcome Definition	Risk Factors Examined	Adjusted for	Results
Foldspang et al. (1992)	Cross-sectional 2,631 women Aged 30-59 years old Aarhus, Denmark	Self-reported SUI during the last year	Parity variables	Age, occupation, menopause, and exposure to abdominal, gynecological-obstetric or urological surgery	Number of childbirths: 1.2 (1.1-1.3) Parity: 1.6 (1.2-2.3) Three or more childbirths: 1.4 (1.1-1.8)
Mommsen et al. (1993)	Cross-sectional study 2,631 women Aged 30-59 years old Aarhus, Denmark	Self-reported SUI during the last year	History of abdominal, gynecological and urological surgery	Age, occupation, parity and menopause	Abdominal: 1.42 (1.03-1.96) Gynecological: 1.69 (1.34-2.15) Urological: 2.60 (1.46-4.63)
Mommsen and Foldspang (1994)	Cross-sectional 2,589 women Aged 30-59 years old Aarhus, Denmark	Self-reported SUI during the last year	BMI	Age, parity, surgical operations, cystitis, menopause, and occupation	Per BMI unit: 1.07 (1.04-1.10)
Nygaard (1997)	Retrospective cohort study 104 women American Olympians Aged 30 t0 63 years old	Self-reported SUI	High-impact (gymnastics and track and field) vs. low-impact sports (swimming), age, BMI, parity, incontinence during Olympic sport	Mutual adjustment	Incontinence during Olympic sport: 11.53 (3.04-43.78) Parity: 1.53 (1.03-2.280

Kuh et al. (1999)	Prospective cohort 1333 women age 48 years U.K.	Self-reported SUI	Childhood enuresis (when six years old), number of children, age at first birth, age at last birth, type of delivery, urinary of kidney infections (15 to 43 years old), menopausal status, BMI at age 43, recent symptoms, medical consultations during last year, education	Mutual adjustment	Age at first birth 30+ years old and vaginal deliveries vs. no births: 3.1 (1.5-6.0) Naturally postmenopausal: 0.54 (0.32-0.91) BMI per 5 units: 1.2 (1.0-1.4) Recent symptoms (quintiles): 1.1 (1.0-1.2) Consultations: 1.4 (1.0-1.9) Education (per degree level): 1.3 (1.2-1.5)
Brown et al. (1999)	Cross-sectional 2763 postmenopausal women younger than 80 years old, mostly Caucasian Baseline data from the Heart and Estrogen/Progestin Replacement Study	Self-reported incontinence during the prior week Stress only vs. no incontinence	Age, ethnicity, number of pregnancies, parity, years since first birth, years since menopause, BMI, waist/hip ratio, overall health status, medical conditions, medication use, number of urinary tract infections during prior year, alcohol consumption, smoking	Mutual adjustment	Caucasian vs. A-A: 2.84 (1.60-5.05) BMI per 5 units: 1.13 (1.01-1.27) Waist-to-hip ratio per 0.1 unit: 1.18 (1.0-1.39)

Hojberg et al. (1999)	Hospital-based Cross-sectional study 7,795 women Cohort sub-study 1781 women Aged 15+ Denmark	Self-reported at least once a week during the last year, at 16 weeks of gestation	Age, parity and mode of delivery, BMI, smoking, previous miscarriages, previous lower abdominal or urological surgery Length of second stage, episiotomy, spontaneous perineal laceration > 3 cm, vacuum extraction, outlet forceps, vaginal laceration, third degree anal sphincter tear, weight of infant > 4,000gr, time since last delivery, oxytocin stimulation, pudendal block	Mutual adjustment Age, BMI, smoking, and mutual adjustment	Primiparous who delivered vaginally vs. nulliparous: 5.7 (3.9-8.3) BMI > 35 vs. 20-30: 2.5 (1.0-6.00) Episiotomy and birthweight > 4,000gr: 3.5 (1.2-10.2)
Moller et al. (2000)	Population-based Case-control study 487 cases 564 controls 40-60 years old Denmark	Self-reported SUI weekly or more by questionnaire	Age, BMI, parity, episiotomy, anal sphincter defect, fetal weight, prior hysterectomy, prior anterior vaginal repair, prior operation for uterine prolapse, hormonal status, use of diuretics, physical activity, and medication	Mutual adjustment	Parity 4+ vs. 0: 7.8 (3.3-18.4) Diuretics: 2.2 (1.2-3.9) BMI highest quartile vs. lowest: 4.2 (2.7-6.7) Hysterectomy: 2.4 (1.6-3.7)
Viktrup and Lose (2001)	Longitudinal cohort study 278 women followed for 5 years after first delivery Aged 17 to 41 years old	Self-reported SUI	Onset and timing of SUI, gestational age, length of the stages of labor, birth weight, head circumference, vacuum extraction, episiotomy	Mutual adjustment	Onset of SUI during the first pregnancy vs. no SUI during the first pregnancy or the 3 months puerperium:

	Denmark				3.8 (1.9-7.5) Onset of SUI during the first puerperium vs. no SUI during the first pregnancy or the 3 months puerperium: 4.5 (1.5-13.2)
Rortveit et al. (2001)	Cross-sectional study 27,900 women 20 years old or older EPINCONT Norway	Self-reported SUI by questionnaire Stress only vs. no incontinence	Parity	Stratification by age	Age group 20-34 years old: Primiparous: 2.7 (2.0-3.5) Grand multiparous (4+): 4.0 (2.5-6.4) Effects of parity seem to disappear with older age
Peyrat et al. (2002)	Cross-sectional study French academic hospital 1700 women Aged 20 to 62 years old (during 1998)	Self-reported current SUI by questionnaire Stress only vs. no incontinence	Age, obesity, pregnancy, previous cesarean delivery, previous vaginal delivery, postpartum incontinence, hysterectomy	No adjustment	Age 40+ 2.18 (1.66-2.87) Pregnancy 2.36 (1.55-3.58) Previous vaginal delivery 2.47 (1.70-3.59) Postpartum incontinence 2.78 (2.14-3.61) Hysterectomy 2.83 (1.93-4.15)

Rortveit et al. (2003) a	Community-based cohort EPINCONT study 15,307 women 20 to 64 years old	Self-reported Stress only vs. no incontinence	Mode of delivery	Age, parity, years since last delivery, and BMI	Vaginal only vs. Cesarean only: 2.4 (1.7-3.2)
Rortveit et al. (2003) b	Community-based cohort EPINCONT study 11,397 women 20 to 64 years old Vaginal deliveries only	Self-reported Stress only vs. no incontinence	Nine delivery variables: high birth weight (4000g or more), gestational age of 40 weeks or more, head circumference of 38 cm or more, breech delivery, injuries in delivery channel, functional delivery disorders, forceps delivery, vacuum delivery, epidural	Age, BMI, parity, and years since last delivery, and the remaining delivery variables	High birth weight: 1.2 (1.1-1.3) Epidural anesthesia: 1.2 (1.0-1.5)
Parazzini et al. (2003)	Case-control study Italy 1062 cases 1143 controls 40 to 88 years old	Self-reported SUI during last month by questionnaire Stress only vs. no incontinence	Age, education, BMI, smoking, alcohol drinking habits, mode of delivery, menopausal status, age at menopause, HRT use, hysterectomy, abdominal surgery, recurrent urinary infections, diabetes, perineal traumas, chronic obstructive pulmonary disease, neurological diseases	Age, education, BMI, obstetric history, HRT use	[Age-adjusted] High BMI; 1.8 (1.3-2.5) 1-2 vaginal births vs. nulliparous: 5.4 (1.9-15.0) Caesarean section vs. no birth: 3.3 (1.1-10.1) Ever HRT use: 0.6 (0.4-0.9) Perineal traumas: 1.9 (1.2-2.9)

Goldberg et al. (2003)	Cross-sectional The Evanston-Northwestern Mothers of Multiples Survey 733 mothers of multiples Mostly Caucasian 22 to 75 years old	Self-reported SUI	Mode of delivery	Age, BMI, parity	Cesarean only vs. at least one vaginal delivery: 0.52 (0.35-0.78)
Chen et al. (2003)	Community-based Cross-sectional study 1,253 women Aged 20 years and older Taiwan	Self-reported SUI with Bristol Female Urinary Tract Symptoms Questionnaire Stress only vs. no incontinence	Age, menopausal status, occupation with heavy lifting, childbirth, vaginal delivery, BMI, previous gynecological surgery, and several medical conditions	Mutual adjustment	Parity 3+ vs. <2: 2.03 (1.09-3.77) Presence of uterovaginal prolapse: 32.95 (12.46-87.14) Previous gynecological surgery: 2.03 (1.13-3.66) Diabetes mellitus history: 3.32 (1.46-7.58)
Dallosso et al. (2003)	Prospective cohort study Leicestershire MRC Incontinence Study, UK 6424 women Aged 40 years and older	Self-reported SUI, at least several times a month, at 1 year follow-up	Age, BMI, physical activity, smoking, food groups and drinks	Mutual adjustment	Obese vs. acceptable weight: 1.74 (1.22-2.48) Carbonated drinks daily or more vs. less than weekly: 1.62 (1.18-2.22) More than daily bread consumption: 0.76 (0.61-0.96)

Hannestad et al. (2003)	Population-based cross-sectional study 27,936 women Age 20 and older EPINCONT study Norway	Self-reported SUI by questionnaire Stress only vs. no incontinence	Smoking, status, number of cigarettes per day, pack years, BMI, low impact physical activity/week, high impact physical activity/week, cups of tea/day, cups of coffee/day, number of glasses of alcoholic beverages/two weeks	Adjustment for age, coughing, wheezing/dyspnoea, and mutual adjustment for the variables of interest	BMI 40+ vs. <25: 2.4 (1.7-3.3) Current <20 cig/day vs. never: 0.8 (0.7-0.9) Low impact PA 3+ vs. <1 hrs/week: 0.8 (0.7-0.9) Cups of tea 3+ vs. 0 per day: 1.3 (1.1-1.5) Cups of coffee 3+ vs. 0 per day: 1.2 (1.1-1.5) 1.3
Fritel et al. (2004)	Retrospective cohort survey 307 women French university hospital Primiparous women	Self-reported stress urinary incontinence 4 years after the first delivery	Age at first delivery, BMI, birth weight, duration of labor, duration of active second stage, mode of delivery, third degree perineal tear, second delivery, urinary leakage before first pregnancy, urinary leakage during the first pregnancy	Mutual adjustment	Leakage before 1st pregnancy: 18.7 (3.6-96.4) Leakage during 1st pregnancy: 2.5 (1.3-4.8) More than 30 years old at 1st delivery: 2.4 (1.4-4.2) Duration of labor of at least 8 hours: 3.1 (1.7-5.7) Cesarean at 1st delivery: 0.3 (0.1-0.9)

Hannestad et al. (2004)	Cross-sectional EPINCONT study Norway Cohort 1: 6021 mothers, 7629 daughters, 332 granddaughters Daughters aged 26 to 40 years Cohort 2: 2104 older sisters, 2426 sisters Younger sisters aged 28 to 40 years	Self-reported Stress only vs. no incontinence	Family history (mother, older sister)	Adjusted for age, BMI, and parity	Mother with SUI: 1.52 (1.28-1.81) Older sister with SUI: 1.8 (1.3-2.3)
Teleman et al. (2004)	Cross-sectional population-based Sweden 2682 women Women's Health in the Lund Area study Aged 50-59	Self-reported SUI, with Bristol Female Lower Urinary Tract Symptoms Questionnaire Sometimes or more vs. no or occasionally	BMI, Elevation of BMI since age 25,current HRT use, alcohol consumption	Mutual adjustment	BMI 30+ vs. <30: 1.55 (1.17-2.05) Elevated BMI by 25% since age 25: 1.69 (1.38-2.06) Current HRT use: 1.47 (1.22-1.78) Moderate alcohol consumption: 0.64 (0.46-0.88)
Jackson et al. (2004)	Cross-sectional study 1,584 Caucasian and African-American women aged 70-79 years The Health, Aging, and Body Composition	Self-reported SUI occurring weekly or more during the past 12 months by questionnaire	Age, race, BMI, parity, hysterectomy, oral estrogen use, diabetes, poor health status, chronic obstructive pulmonary disease, stroke, arthritis, and depressive symptoms	Adjusted for recruitment site, alternative anthropomorphic measures, and the other factors	Chronic obstructive pulmonary disease: 5.6 (1.3-23.2) Caucasian vs. African-American: 4.1 (2.5-6.7) Current oral

	Study				estrogen use: 2.0 (1.3-3.1) BMI (per 5 units): (1.1-1.6)
Handa et al. (2004)	Cross-sectional study 1293 women scheduled for hysterectomy The Maryland Women's Health Study <30 to 60+ years old	Self-reported SUI during last month, with the Urinary Symptom Scale for Women questionnaire Some of the time or more vs. not at all or little of the time	Age, race, BMI, smoking, UL as primary diagnosis, uterine weight, parity, route of delivery	Mutual adjustment	All women: Parity 1-3 vs. 0: 1.96 (1.28-3.00) Parity 4+ vs. 0; 3.10 (1.82-5.30) Caucasian vs. African-American: 1.49 (1.15-1.95) BMI (per 1 unit): 1.06 (1.04-1.08) Parous women: Cesarean delivery only vs. at least one vaginal: 0.60 (0.39-0.93) Parity 4+ vs. 1-3: 1.55 (1.06-2.26) Caucasian vs. African-American: 1.52 (1.15-2.02) BMI (per 1 unit): 1.06 (1.04-1.08)
Schytt et al. (2004)	Cohort study 2390 women followed one year after childbirth Median age 29 years old	Self-reported SUI during the last week	Age, education, marital status, native language, number of children, mode of delivery for previous	Mutual adjustment	Parity: 1.4 (1.1-1.8) Constipation 4-8 weeks after

	Sweden		pregnancies, and variables related to the current pregnancy (constipation, urinary incontinence, mode of delivery, presentation, infant birth weight, infant head circumference, spontaneous perineal rupture, episiotomy, smoking)		childbirth: 1.4 (1.1-1.90 Urinary incontinence 4-8 weeks after childbirth: 5.7 (4.3-7.6) Cesarean section vs. vaginal delivery for current pregnancy: 0.5 (0.3-0.9) Age > 35 years old: 1.5 (1.0-2.1) Obesity: 1.5 (1.0-2.2)
Han et al. (2005)	Cross-sectional study 769 women Aged 30 and older South Korea	Self-reported SUI during the past 12 months	Age, occupation, alcohol consumption, smoking status, physical exercise, total number of vaginal deliveries, menopausal status, use of postmenopausal hormone therapy, diabetes, hypertension, hysterectomy	Mutual adjustment	Blue collar vs. white collar: 3.23 (1.21-8.58) Vaginal delivery 4+ vs. 0-1: 5.33 (2.81-10.09) Waist circumference 90+ cm vs. <78 cm: 6.07 (3.23-11.40)
Rohr et al. (2005)	Population-based cross-sectional study 5795 women 46+ years old Denmark	Self-reported SUI during last month	Age, BMI, parity, use of diuretics, HRT, previous stroke, previous myocardial infarction, previous hysterectomy, diabetes, Parkinson,	Mutual adjustment	Age 80+ vs. <60: 2.39 (1.97-2.90) BMI 30+ vs. <25: 1.78 (1.40-2.27) Parity

			chronic lung disease		3+ vs. 0: 1.27 (1.04-1.55) Chronic lung disease: 1.65 (1.35-2.02) Stroke: 1.80 (1.19-2.72) Use of diuretics: 1.22 (1.06-1.42)
Goldberg et al. (2005)	Cross-sectional 271 identical twin sister pairs The Evanston-Northwestern Twin sister study 15 to 85 years old	Self-reported SUI with the Pelvic Floor Distress Inventory and Incontinence Impact Questionnaire	Age, number of pregnancies, total parity, smoking history, paternal and maternal BMI, menopause, duration of the second stage of labor, asthma, hysterectomy; birth mode (vaginal delivery vs. cesarean section), weight of largest baby; episiotomy, forceps	Mutual adjustment	Age 40-49 vs. < 40: 2.3 Menopause: 1.49 Parity 2+ vs.0: 4.33 BMI >30: 3.39 Among parous-parous twin pairs: Vaginal delivery vs. cesarean section: 2.28 (1.14-4.55)
Song et al. (2005)	Cross-sectional 4684 women Age 20 years and older Fuzhou, China	Self-reported SUI, with Bristol Female Lower Urinary Tract Symptoms Questionnaire	Age, BMI, smoking status, parity, route of delivery (only Cesarean, at least one vaginal), episiotomy (during the second stage of labor), education, postmenopausal status, diabetes mellitus, hypertension, occupation, constipation, fetal	Mutual adjustment	Age (10 yrs groups): 1.3 (1.1-1.4) Vaginal delivery: 3.0 (1.9-4.7) Parity > 2: 2.1 (1.5-2.9) Hypertension: 2.7 (1.4-5.6) Constipation: 2.6 (1.8-3.8) Alcohol use

			birthweight, alcohol consumption		(drinks/week): 4.7 (1.1-20.2) Episiotomy: 1.7 (1.4-2.0) Higher BMI (75th percentile or more): 1.8 (1.5-2.2) Unskilled worker: 0.7 (0.5-0.8)
Hendrix et al. (2005)	Multicenter, double-blind, placebo-controlled clinical trials Women's Health Initiative 23,296 postmenopausal women aged 50 to 79 years old	Incidence and worsening (of amount, of frequency, or of degree of bother) of self-reported stress urinary incontinence (during the last year) Stress only vs. no incontinence	Menopausal hormone therapy (MHT): estrogen + progestin (conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), estrogen alone	Age, years since menopause, ethnicity, BMI, prior MHT use and duration, smoking, history of diabetes, asthma, emphysema, or stroke, age at first birth, parity, breast feeding, use of diuretics, use of other medications, alcohol use	CEE + MPA: Incidence: 1.87 (1.61-2.18) Worsening of frequency: 1.41 (1.21-1.64) CEE: Incidence: 2.15 (1.77-2.62) Worsening of amount: 2.18 (1.69-2.81) Worsening of degree of bother: 1.65 (1.42-1.93)
Manonai et al. (2005)	Population-based cross-sectional study 1,126 women Mostly premenopausal Aged 15 to 95 years old Rural area Thailand	Self-reported SUI within the previous month	Marital status, occupation, menopausal status, history of childbirth Among parous women: parity and route of delivery	Mutual adjustment	Peri/postmenopausal vs. premenopausal: 1.50 (1.08-2.080 History of childbirth: 2.45 (1.55-3.88) Among parous

					women: Vaginal vs. Cesarean: 1.89 (1.25-2.87)
McGrother et al. (2006)	Prospective cohort study Leicestershire MRC Incontinence Study 20,247 women Age 40 to 98 years old	Self-reported SUI by postal questionnaire occurring monthly or more validated against pad test and diary Baseline and 1 year follow-up	Parkinson's disease, multiple sclerosis, epilepsy, spinal cord injury, dementia, osteoporosis, hypertension, angina, heart attack, blocked leg arteries, deep-vein thrombosis, Raynaud's disease, diabetes, rheumatoid arthritis, depression, joint pain/stiffness, breathlessness, ankle swelling, balance/dizziness, falls, hearing problems, memory problems, vision problems, stroke, minimal trauma fracture, cystitis, bowel symptoms, hay fever, dermatitis or eczema, asthma, physical impairment in terms of activities of daily living, BMI	Age, parity, and the other variables	Prevalence: General health poor vs. excellent/very good: 2.0 (1.3-3.1) ADL 3 vs. 1 (best): 1.8 (1.4-2.3) BMI obese vs. acceptable: 1.7 (1.4-2.1) Age (10 years increase): 0.8 (0.7-0.8) Depression: 1.4 (1.1-1.7) Memory: 1.4 (1.1-1.7) Breathlessness: 1.4 (1.1-1.8) Asthma: 1.5 (1.1-1.9) Cystitis: 1.5 (1.2-1.90 Bowel straining: 1.5 (1.2-1.9) Parity 3+ vs. 0; 1.7 (1.2-2.3)

					Incidence: BMI obese vs. acceptable: 2.3 (1.6-3.3) Cystitis: 1.9 (1.3-2.7) Age (10 years increase): 0.8 (0.6-0.9)
Thom et al. (2006)	Population-based cohort study 2,109 randomly selected middle-aged and older women RRISK study Between 40 and 69 years old as of January 1, 1999 Kaiser Permanente Medical Care Program of Northern California	Self-reported SUI during the last year, by questionnaires and interview	Race/Ethnicity	Age, parity, hysterectomy, current estrogen use, BMI, menopausal status, and diabetes	African-American vs. Caucasian: 0.36 (0.23-0.57) Asian vs. Caucasian: 0.54 (0,34-0,84)

CHAPTER II

STATEMENT OF SPECIFIC AIMS

Risk Factors Associated with Subtypes of Uterine Leiomyomata

No population-based epidemiological studies have investigated if the associations between risk factors and UL subtypes are similar. The association of age at first birth and age at first being detected infertile with the location of UL as an outcome has been examined only as a secondary analysis in a practice-based case-control study (Faerstein et al. 2001 a). The research described in this dissertation included premenopausal African-American and Caucasian women from the baseline phase of the NIEHS Uterine Fibroid Study. The USF study combines the strengths of having detailed information on the location of UL with the inclusion of a large number of African-American women.

The risk factors considered were age, age at menarche, parity, BMI, current cigarette smoking status, and current physical activity. When examining parity, full-term births after age 24 were considered the primary variable (Baird et al. 2003). Separate investigations were performed for each ethnic group. The UL subtypes considered were: submucosal UL (i.e. at least one submucosal UL present), intramural/subserosal UL (i.e. focal UL present, but only of intramural or subserosal type), and diffuse only (i.e. only a diffuse heterogeneous echopattern present).

The specific aims were to investigate for each ethnic group if the associations between a risk factor and the three UL subtypes (submucosal UL, intramural/subserosal

UL, and diffuse only) are similar, or equivalently if the three corresponding odds ratios are equal. The specific study questions considered were:

Are the associations similar between age and the three UL subtypes among the African-American premenopausal women? Are the associations similar between age and the three UL subtypes among the Caucasian premenopausal women?

Are the associations similar between age at menarche and the three UL subtypes among the African-American premenopausal women? Are the associations similar between age at menarche and the three UL subtypes among the Caucasian premenopausal women?

Are the associations similar between any full-term births after age 24 and the three UL subtypes among the African-American premenopausal women? Are the associations similar between any full-term births after age 24 and the three UL subtypes among the Caucasian premenopausal women?

Are the associations similar between BMI and the three UL subtypes among the African-American premenopausal women? Are the associations similar between BMI and the three UL subtypes among the Caucasian premenopausal women?

Are the associations similar between smoking status and the three UL subtypes among the African-American premenopausal women? Are the associations similar between smoking status and the three UL subtypes among the Caucasian premenopausal women?

Are the associations similar between physical activity and the three UL subtypes among the African-American premenopausal women? Are the associations similar between physical activity and the three UL subtypes among the Caucasian premenopausal women?

Self-Reported Urinary Symptoms Associated with Uterine Leiomyomata

No population-based observational studies have assessed the association between the characteristics of UL and SUI. The research described in this dissertation included African-American and Caucasian premenopausal women from the first follow-up of the NIEHS Uterine Fibroid Study. This study combines the strengths of detailed information on the size and location of UL with the inclusion of a large number of African-American women, who are at increased risk of UL compared with Caucasian women.

The proposed aims were to:

1. Estimate the association between the presence of UL and SUI, and assess if this association differs by ethnicity and parity.
2. Estimate the association between the size of the largest UL (small, medium, large) and SUI, and assess if this association differs by ethnicity and parity.
3. Estimate the association between the presence of a large (≥ 4cm diameter) anterior UL in a non-retroverted uterus and SUI, and assess if this association differs by ethnicity and parity.
4. Estimate the association between the presence of a medium/large (≥ 2cm diameter) anterior UL in a non-retroverted uterus and SUI, and assess if this association differs by ethnicity and parity.
5. Estimate the association between the size of uterus (small, medium, large, very large) and SUI, and assess if this association differs by ethnicity and parity.

The presence of a large anterior UL in a non-retroverted uterus is very likely to exert pressure on the bladder; by contrast the presence of a large anterior UL in a retroverted uterus may have much lesser impact on the bladder, if any.

The interest in effect modification by ethnicity was motivated by the African-American women being at an increased risk of UL, but at a decreased risk of SUI when compared with Caucasian women. The interest in the effect modification by parity was motivated by the fact that pregnancies loosen the pelvic floor.

The specific study questions considered were:

Are premenopausal women with UL more likely to report symptoms of SUI than premenopausal women without UL? Does this association differ by ethnicity or parity?

Are premenopausal women with large (≥ 4 cm diameter) UL more likely to report symptoms of SUI than premenopausal women without UL? Are premenopausal women with medium (2-4 cm) UL more likely to report symptoms of SUI than premenopausal women without UL? Are premenopausal women with small (<2 cm) UL more likely to report symptoms of SUI than premenopausal women without UL? Do these associations differ by ethnicity or parity?

Are premenopausal women with large (≥ 4 cm diameter) anterior UL in a non-retroverted uterus more likely to report symptoms of SUI than premenopausal women without UL? Are premenopausal women with other types of UL more likely to report symptoms of SUI than premenopausal women without UL? Do these associations differ by ethnicity or parity?

Are premenopausal women with medium/large (≥ 2 cm diameter) anterior UL in a non-retroverted uterus more likely to report symptoms of SUI than premenopausal women without UL? Are premenopausal women with other types of UL more likely to report symptoms of SUI than premenopausal women without UL? Do these associations differ by ethnicity or parity?

Are premenopausal women with very large uterine size (above the 83rd percentile of uterine volume) more likely to report symptoms of SUI than premenopausal women with small uterine size (lower tertile of uterine volume)? Are premenopausal women with large uterine size (67th to 83rd percentile of uterine volume) more likely to report symptoms of SUI than premenopausal women with small uterine size (lower tertile of uterine volume)? Are premenopausal women with medium uterine size (middle tertile of uterine volume) more likely to report symptoms of SUI than premenopausal women with small uterine size (lower tertile of uterine volume)? Do these associations differ by ethnicity or parity?

CHAPTER III

METHODS

Study Design and Study Population

The investigation used data from the NIEHS Uterine Fibroid Study, a study specifically designed to reduce detection bias by randomly selecting women and screening them for UL using a standardized protocol, in contrast with prior studies that have identified women based on clinical diagnosis. The study was approved by the Humans Subject's Review Boards at the NIEHS and at George Washington University.

Women, aged 35 to 49 years old, were selected randomly from a computerized list of the members of a health plan at its Washington, DC, site. The prepaid urban health plan was chosen because of the overall characteristics of its membership. About half of the members were African-American, and the health plan had a broad socioeconomic base. The specific age range was selected because it covers the late premenopausal years (when UL are most prevalent) and because ultrasound screening can be used for the majority of the women within this age range, since a small proportion of them is expected to be surgically or naturally menopausal.

A random sample of 2,384 health plan records of women aged 35-49 with telephone contact information was obtained. The randomly selected women were sent a letter describing the study. A phone call was attempted to confirm their eligibility with respect to gender, age (35 to 49 years old), health plan membership at the Washington, DC, site, and ability to complete data collection in English. A small proportion (129 (5%)) could not be

reached, 150 (6%) refused screening for eligibility, and 3 were not contacted due to error. Of the 2102 women screened, 316 (15%) were ineligible, primarily because they did not obtain care at the Washington, DC health plan site. Of the 1786 eligible women, 335 (19%) refused to participate. Also prior to data collection contact was lost with 17 (1%) who initially agreed to participate and 4 who were undecided about participation. At the end, 1430 women, constituting 80% of the eligible women, participated in the study. The baseline phase was conducted between 1996 and 1999.

Out of the 1245 premenopausal women from the baseline phase of the NIEHS Uterine Fibroid Study 1,229 have been followed for symptoms including SUI. The first follow-up was conducted between 2001-2002.

Baseline Data Collection

A mail questionnaire which took about 30 minutes to complete was used to collect data regarding medical history (Section A), symptoms (Section B), employment and household exposures (Sections C and D), pets (Section E), household pests (Section F), alcohol use (Section G), demographics (Section H), and stress (Section I).

The phone interview, which lasted about an hour, collected information about age (Section A), occupational history (Section B), menstruation and douching (Section C), contraceptive history (Section D), hormone medication history (Section E), pregnancy history (Section F), residential history and childhood factors (Section G), physical activity (Section H), smoking history (Section I), hair products (Section J), nonprescription medication and sleep patterns (Section K), and fibroid-related medical history (Section L). The last section complemented Section A of the mail questionnaire, and included information

about medical procedures or conditions such as tubal ligation, pelvic surgeries, UL diagnosis and treatment, and ultrasound/sonograms.

The women were told that the goal of the research was to study UL. All interviewers were trained by the study interviewer supervisor on how to conduct the interviews and record responses. Interviewers were unaware of the UL status of the study participant when they conducted most of the phone interview. All data were double entered.

The determination of UL status involved, as a first step, a self-reported UL diagnosis at the telephone interview. The question used was: "Have you ever been told by a doctor or other health professional that you have uterine fibroid tumors or a leiomyoma, a benign tumor of the uterus or womb?" Women, who answered affirmatively and did not report misdiagnosis in subsequent questions about diagnostic, follow-up examinations, treatment, and persistence of UL, were classified as having a previous diagnosis of UL.

Women were classified as premenopausal if they had a menstrual period or were pregnant or breast-feeding during the previous 12 months.

For premenopausal women who had had a pelvic ultrasound examination recently at the health plan, that examination was used to assess the UL status. For the remaining premenopausal women, a subsequent pelvic ultrasound examination at the primary care site provided further UL status assessment for those with a previous diagnosis, and allowed the identification of undiagnosed UL for those with no previous diagnosis of UL. Women who failed to visit the clinic for an ultrasound examination but reported a previous diagnosis were included as UL cases, but those without ultrasound and no prior diagnosis were left with an undefined UL status.

The study ultrasound included both a transabdominal and a transvaginal ultrasound. The transabdominal ultrasound allowed identification of UL in the upper uterus, which may be difficult to detect with a transvaginal ultrasound.

Both the transabdominal and transvaginal ultrasound examinations were performed by sonographers who were certified by the American Registry of Diagnostic Medical Sonographers, under the supervision of a radiologist with fellowship training in sonography. A single radiologist reviewed any questionable sonograms. The examinations were performed with ultrasound units ATL HDI 9 (ATL, Bothell, Washington), Acuson 128 XP (Siemens, Issaquah, Washington), and Diasonics DRF 400 (General Electric, Milwaukee, Wisconsin), using transabdominal ultrasound probes (3.5-5.0 MHz) and transvaginal ultrasound probes (5.0-7.0 MHz). The sonographers filled out a study-specific data collection form that included data on uterine size, uterine contour, heterogeneity of the echo pattern, number of focal UL, the size and location of the two largest UL (if more than 2 cm in diameter), and the size of the three largest submucosal UL.

Sonogram data, including the size and location of UL when present were available for 1083 women (87% of the premenopausal participants). About 20% of sonograms from the NIEHS Uterine Fibroid Study indicated a diffuse heterogeneous echopattern only (Wegienka et al. 2003). This echopattern was extensive (rather than occurring only along the endometrial stripe as with adenomyosis). Women with this pattern were classified as having "diffuse only". There was also a very small number of participants with only submucosal UL, which prevented the categorization of women with focal UL into "submucosal only", "nonsubmucosal only", and "both submucosal and nonsubmucosal". Because of these

reasons the UL subtype was categorized as “diffuse only”, “intramural/subserosal UL”, and “submucosal UL”.

Follow-up Data Collection

A computer-assisted telephone interview was used to collect data on employment, medical insurance, and general health status (Section A), pregnancy history since enrollment (Section B), medical history (Section C), new UL diagnosis (Section D), sonograms and MRI (Section E), major UL treatment and hysterectomy (Section F), menstruation (Section G), symptoms (Section H), medication (Section I), and demographics (Section J).

The urinary symptoms investigated were the self-reported (at the follow-up) presence of SUI. More precisely the following question from Section H from the follow-up phone questionnaire was used: “During the [last 12 months/12 months before your last period/12 months before the (Procedure)], have you ever had urine leak when you cough or sneeze?” The “procedure” mentioned in the question was the procedure reported in Section F (Major UL treatment and hysterectomy) of the phone interview, and it was one of the following: myomectomy, hystereoscopic resection, uterine artery embolization, or hysterectomy.

For women currently menstruating, who did not undergo any of the procedures listed above, the time frame for the question was “last 12 months”. For those without a period in the last two months the time frame for the question was “12 months before your last period”. For those who underwent surgery the time frame was “12 months before the procedure”. Procedure had precedent (i.e. “12 months before the procedure” was asked) if women were still menstruating and have had one of the surgical procedures listed.

Data Analysis for Paper 1

We defined four possible outcome groups:

1) "No UL",
2) "Submucosal UL" (i.e. at least one submucosal focal UL present, with or without other UL),
3) "Intramural/subserosal UL" (i.e. focal intramural or subserosal UL present, and no submucosal UL), and
4) "Diffuse only" (defined in this study as a diffuse heterogeneous echo pattern with no measurable focal UL).

Risk factors analyzed for the current study included age at ultrasound examination, age at menarche, having at least one full-term pregnancy after age 24, body mass index (BMI, kg/m^2, categorized as <25, 25+), current physical activity (low/medium vs. high/very high), and current cigarette smoking (yes, no). Earlier work with the NIEHS UFS showed that pregnancies early in life were not associated with UL risk, but full-term pregnancies after age 24 were inversely associated with risk (Baird and Dunson 2003). The physical activity variable was categorized as in Baird et al. 2006, based on self-reported hours/week of vigorous activities, moderate activities or walking, and the estimated metabolic units associated with each type of activity.

Separate analyses were performed for each ethnic group (African-American and Caucasian women), and for all women combined. Ethnicity was determined by self-report. Univariate analyses were performed to describe the distributions of exposures and outcomes, and assess missing data.

The models of interest were the race-specific polytomous logistic regression models that included all six risk factors. A polytomous logistic regression model for all data combined was also performed. The later model included ethnicity in addition to the six risk factors of interest. The referent group for the polytomous logistic regression models was "no UL". Age and age at menarche were modeled as continuous variables after confirming the assumption of linearity. Tests of equal effects across UL subtypes were performed for each variable of interest in all models, using Wald chi-squared tests of corresponding contrasts. All analyses were performed using the SAS software package (SAS v.9.1; SAS Institute, Inc., Cary, North Carolina).

Data Analysis for Paper 2

The outcome variable considered was the presence of self-reported SUI ("yes"/"no"). UL status was classified according to:

1) The presence of any UL: "any UL" vs. "no UL"
2) The size of the largest UL: "no UL", "small (< 2cm) UL", "medium (2-4cm) UL", and "large (≥ 4cm) UL)"
3) The presence of a large (≥ 4cm) anterior UL in a non-retroverted uterus: "no UL", "large (≥ 4cm) anterior UL in non-retroverted uterus", and "other UL"
4) The presence of a medium/large (≥ 2cm) anterior UL in a non-retroverted uterus: "no UL", "medium/large (≥ 2cm) anterior UL in non-retroverted uterus", and "other UL"

5) Uterine size: "small (lowest 33% of overall uterine volume distribution)", "medium (middle 33%)", "large (those in 67th to 83rd percentile)", and "very large (those above the 83rd percentile)".

The uterine volume was calculated using the prolate ellipsoid formula (0.52 x length x width x anterior/posterior diameter). The actual cut points used to define the four categories of uterine size were: 91.4 cm^3 (the 33rd percentile), 147.8 cm^3 (the 66th percentile), and 206.5 cm^3 (the 83rd percentile).

Potential confounders, selected based on a review of the literature regarding risk factors for UL and SUI, included age at the reference date (continuous or categorized as <40, [40,45), [45,50), 50+), ethnicity (African-American, Caucasian), BMI at baseline (kg/m^2, categorized as <25, [25,30), [30,35), 35+), and the number of deliveries prior to the reference date (categorical, 0, 1, 2, 3+). A composite variable involving the number and the type of deliveries (none, only C-section deliveries, 1 vaginal delivery, 2 vaginal deliveries, 3+ vaginal deliveries) was also evaluated as a potential confounder, but was not used since results were comparable with those adjusted for the number of deliveries.

Univariate analyses were performed to describe the distributions of exposures and outcomes, and assess missing data. Given the prevalence of the outcome under study (about 50% of the participants have reported SUI), odds ratios are an overestimate for the relative risk. Therefore, we used linear risk models to estimate prevalence differences (PD) and corresponding 95% confidence intervals (CI) (Spiegelman and Hertzmark, 2005). Separate linear risk models were used to evaluate the association between each of the five variables of interest and self-reported SUI. We estimated crude, ethnicity-adjusted, and fully-adjusted PDs with 95% CIs, with the fully-adjusted estimates from linear risk models that included

age at reference (continuous), ethnicity, BMI, and number of deliveries. All model estimates were evaluated to confirm that predicted prevalences were between 0 and 1.

Ethnicity was evaluated as a potential effect modifier since African American women are at increased risk of UL but at decreased risk of SUI compared with Caucasians. In addition we evaluated effect modification by parity (nulliparous vs. parous) as pregnancy loosens the pelvic floor. Formal evaluation of effect modification by ethnicity and parity was performed using likelihood ratio tests ($\alpha = 0.10$). All analyses were performed using the SAS software package (SAS v.9.1; SAS Institute, Inc., Cary, North Carolina).

REFERENCES

Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology. 2003 Mar;14:247-250.

Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. Association of physical activity with development of uterine leiomyoma. Am J Epidemiol. 2007 Jan 15;165:157-163.

Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol. 2005 Aug 1;162:199-200.

Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, Schectman JM, Hartmann KE. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101:431-437.

CHAPTER IV

PAPER 1: RISK FACTORS ASSOCIATED WITH SUBTYPES OF UTERINE LEIOMYOMATA

Abstract

OBJECTIVE: To compare risk factors for each of three uterine leiomyomata (UL) subtypes (submucosal UL, intramural/subserosal UL, and diffuse only) among premenopausal African-American and Caucasian women.

METHODS: This cross-sectional study used data from 986 premenopausal aged 35 to 49 years old that were enrolled in the National Institute of Environmental Health Sciences Uterine Fibroid Study. Participants were randomly selected from the membership list of a Washington, DC health plan, and data were collected between 1996 and 1999. UL were identified and subtyped based on transabdominal and transvaginal ultrasound examinations. Polytomous logistic regression models were used to estimate associations between six potential risk factors and UL subtypes within each ethnic group and for all women combined.

RESULTS: For both African-American and Caucasian women, age at ultrasound examination, age at menarche, body mass index, and current physical activity had similar associations across the three UL subtypes. Inverse associations with pregnancies after age 24 appeared to be stronger for the submucosal UL subtype than for the other two subtypes (aOR=0.59 95% CI: 0.35, 1.01 in African-Americans and aOR=0.25 95% CI: 0.10, 0.58 in Caucasians). Current smoking was positively associated with the diffuse only subtype

(aOR=1.97 95% CI: 1.11, 3.51 in African-Americans, aOR=3.00 95% CI: 1.07, 8.38 in Caucasians), but was not associated with focal UL subtypes in either ethnic group.

CONCLUSIONS: Despite possible histopathologic differences that have been noted in the literature, the two focal UL subtypes appeared to have similar risk factor profiles for the factors examined. In contrast, the diffuse only subtype appeared to have a distinctive risk profile with regard to current smoking. Further study of the epidemiological and histopathologic correlates of diffuse heterogeneity seen with uterine ultrasound are needed.

Introduction

Uterine leiomyomata (UL) are the most prevalent solid tumors among women in the United States (Flake et al. 2003). Based on cross-sectional screening for UL among women aged 35 to 49 years old, the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study estimated that more than 80% of African-American women and that about 70% of Caucasian women develop UL by age 50 (Baird et al. 2003). Although only 20 to 50% of women with UL experience related symptoms (Stovall 2001), the economic impact of UL is considerable. Estimates for the direct cost of treating UL have been as high as $2.15 billion per year (Flynn et al. 2006).

UL are benign tumors derived from smooth muscle cells in the uterine myometrium. UL are sub-classified as submucosal, intramural, or subserosal according to their position within the uterine myometrial wall. Specifically, submucosal UL lie immediately adjacent to or protrude into the endometrial cavity; intramural UL are contained within the muscle layer; and subserosal UL lie immediately adjacent to or protrude into the peritoneal cavity (Stewart 2001). Although there is evidence that differences exist beyond the position of UL subtypes (Marugo et al. 1989, Brosens et al. 1998, Brosens 2003), published research on risk factors

for UL subtypes is limited to a small secondary analysis of subtype-specific associations with parity and infertility in a practice-based case-control study of 111 women with known location of UL (Faerstein et al. 2001 a). The objective of this study was to compare risk factors for UL subtypes among premenopausal African-American and Caucasian women in the NIEHS Uterine Fibroid Study.

Methods

The NIEHS Uterine Fibroid Study (UFS) was specifically designed to reduce detection bias by randomly selecting women for UL screening using a standardized protocol, in contrast with most studies that determined UL status based on clinical diagnosis only. The study was approved by Humans Subject Review Boards at the NIEHS and George Washington University.

Women aged 35 to 49 years old were selected randomly from a computerized list of health plan members at a Washington, DC, site. The prepaid urban health plan was chosen because about half of its members were African-American, and it had a broad socioeconomic base. The specific age range was selected because it covers the late premenopausal years (when UL are most prevalent), and because relatively few women in this age group were expected to be surgically or naturally menopausal.

A random sample of 2,384 health plan records of women aged 35-49 with telephone contact information was obtained. The randomly selected women were sent a letter describing the study, which was followed by a phone call to confirm eligibility with respect to gender, age, health plan membership at the Washington, DC, site, and ability to complete data collection in English. A small proportion (129 (5%)) could not be contacted, 150 (6%)

refused screening for eligibility, and 3 were not contacted due to error. Of the 2,102 women screened, 316 (15%) were ineligible, primarily because they did not obtain care at the Washington, DC health plan site. Of the 1,786 eligible women, 335 (19%) refused to participate, and 24 (1%) were lost to contact prior to data collection. In total, 1,430 women, constituting 80% of those determined to be eligible, participated in the UFS.

Baseline data collection for the UFS was conducted between 1996 and 1999 using a mail questionnaire that took about 30 minutes to complete, and a phone interview, which lasted about an hour. All interviewers were trained, and all data were double entered and verified.

The study was designed to evaluate UL status by ultrasound for all premenopausal women with intact uteri, and this analysis is limited to that group. Women were classified as premenopausal if they had a menstrual period or were pregnant or breast-feeding during the previous 12 months. If participants had had a recent pelvic ultrasound at the clinic we abstracted data from that to determine UL status (sonograms within 5 years that showed UL were used; sonograms within 2 years that showed "No UL" were used). All others were asked to have a study ultrasound examination.

The study ultrasound included both transabdominal and transvaginal examinations, with the former used to facilitate identification of UL in the upper uterus. Examinations were performed by sonographers certified by the American Registry of Diagnostic Medical Sonographers, under the supervision of a radiologist with fellowship training in sonography. A single radiologist reviewed all questionable sonograms. The examinations were performed with ultrasound units ATL HDI 9 (ATL, Bothell, Washington), Acuson 128 XP (Siemens, Issaquah, Washington), and Diasonics DRF 400 (General Electric, Milwaukee, Wisconsin),

using transabdominal ultrasound probes (3.5-5.0 MHz) and transvaginal ultrasound probes (5.0-7.0 MHz). Sonographers filled out a study-specific data collection form that included data on uterine size, uterine shape, diffuse heterogeneous echo pattern (yes/no), number of focal UL, the size and location of the two largest UL (if more than 2 cm in diameter), and the size of the three largest submucosal UL.

We defined four possible outcome groups: 1) no UL, 2) submucosal UL (i.e. at least one submucosal focal UL present, with or without other UL), 3) intramural/subserosal UL (i.e. focal intramural or subserosal UL present, and no submucosal UL), and 4) diffuse only (defined in this study as a diffuse heterogeneous echo pattern with no measurable focal UL).

Women were eligible for the current study if they were premenopausal African-American or Caucasian participants in the baseline phase of NIEHS UFS (n = 1,144). Women were excluded if they were missing UL subtype data (n = 158); therefore the final population included 986 women (86% of those eligible).

Risk factors analyzed for the current study included age at ultrasound examination, age at menarche, having at least one full-term pregnancy after age 24, body mass index (BMI, kg/m^2, categorized as <25, 25+), current physical activity (low/medium vs. high/very high), and current cigarette smoking (yes, no). Earlier work with the NIEHS UFS showed that pregnancies early in life were not associated with UL risk, but full-term pregnancies after age 24 were inversely associated with risk (Baird and Dunson 2003). The physical activity variable was categorized as in our previous analysis (Baird et al. 2006), based on self-reported hours/week of vigorous activities, moderate activities or walking, and the estimated metabolic units associated with each type of activity.

Separate analyses were performed for each ethnic group (African-American and Caucasian women), and for all women combined. Ethnicity was determined by self-report. Univariate analyses were performed to describe the distributions of exposures and outcomes, assess missing data, and identify potential outliers.

The models of interest were the race-specific polytomous logistic regression models that included all six risk factors. A polytomous logistic regression model for all data combined was also performed. The later model included ethnicity in addition to the six risk factors of interest. The referent group for the polytomous logistic regression models was "no UL". Age and age at menarche were modeled as continuous variables after confirming the assumption of linearity. Tests of equal effects across UL subtypes were performed for each variable of interest in all models, using Wald chi-squared tests of corresponding contrasts. All analyses were performed using the SAS software package (SAS v.9.1; SAS Institute, Inc., Cary, North Carolina).

Results

Characteristics of the sample of 986 premenopausal women included in the current study are presented in Table 4.1. More African-American women than Caucasian women had early (< 12 years old) menarche (27% vs. 19%), had a high BMI (mean BMI 30.4 vs. 25.9 kg/m^2, with 43% vs. 18% classified as obese), were current smokers (29% vs. 8%), reported full term pregnancies after age 24, and reported low or medium physical activity.

Overall, 63% of the analysis sample had UL, including 72% of African Americans and 50% of Caucasians (Table 4.1). In both racial groups, about 20% of women with UL

were classified as having diffuse only, about 20% had submucosal UL, and the remaining 60% had intramural/subserosal UL.

African-American women had a higher prevalence of all three UL subtypes than Caucasian women, but the association with ethnicity was somewhat weaker for the diffuse only subtype (adjusted odds ratio (aOR) 1.86, 95% confidence interval (95% CI): 1.14, 3.06, adjusted for age, age at menarche, full term pregnancies after age 24, BMI, physical activity and current smoking) than for submucosal UL (aOR=3.30 95% CI: 2.05, 5.34) and intramural/subserosal UL (aOR=2.72 95% CI: 1.94, 3.83). However, the three estimated adjusted ORs were not statistically different from each other ($p = 0.157$).

For most potential risk factors, associations were similar for all three subtypes of UL (Figure 4.1, Table 4.2). For both African Americans and Caucasians, age was positively associated with all three UL subtypes, without clear differences in the magnitude of subtype-specific associations (p-values for differences among UL subtypes estimated adjusted ORs were 0.438 and 0.084 for African American and Caucasians, respectively, see Table 4.3). Age at menarche and physical activity were inversely associated with all three UL subtypes among women in both ethnic groups, and there was no significant difference between subtypes (all p-values for difference > 0.500, see Table 4.3). Subtype-specific associations with BMI also were comparable within ethnic groups; however, associations were positive among African Americans and weak among Caucasians, consistent with previous studies of UL in general (Marshal et al. 1998 a, Wise at al. 2005, Baird et al. 2006).

Pregnancies after age 24 were inversely associated with submucosal UL in both African-Americans and Caucasians (aOR=0.59 95% CI: 0.35, 1.01 and aOR=0.25 95% CI: 0.10, 0.58 respectively), while the associations were weaker for the other UL subtypes in

both ethnic groups. There was even a non-significant positive association with the diffuse only subtype for Caucasians (aOR=1.58 95% CI: 0.76, 3.28), where the effects across UL subtypes were significantly different ($p < 0.001$).

Associations with smoking also differed across UL subtypes, and patterns were similar between African Americans and Caucasians. Specifically, smoking was positively associated with the diffuse only subtype (aOR=1.97 95% CI: 1.11, 3.51 in African Americans, aOR=3.00 95% CI: 1.07, 8.38 in Caucasians), but was not associated with submucosal or intramural/subserosal UL. P-values for differential effects across UL subtypes were 0.014, 0.036, and 0.002 for African Americans, Caucasians and all women combined, respectively.

Discussion

The NIEHS Uterine Fibroid Study used ultrasound to screen for UL, which allowed for outcome categorization according to UL subtypes. We examined the association of six putative risk factors with each of the three UL subtypes examined, using separate analyses for African-American and Caucasian women. Within each ethnic group age, age at menarche, BMI, and physical activity had very similar associations across UL subtypes. There was more variation among subtypes in association with pregnancies after age 24 especially for Caucasians, and current smoking had significant differential subtype-specific associations in both ethnic groups. The effect was different for the diffuse only subtype than for focal UL (submucosal and intramural/subserosal UL) subtypes.

Although UL subtypes may develop in response to different environmental or endogenous factors, this is the first epidemiological study to systematically evaluate risk

factors for UL subtypes. We examined submucosal UL as a separate subtype based on evidence that the subendometrial myometrium (i.e. the junctional zone adjacent to the endometrium) is structurally and functionally different from the outer myometrium (Brosens 2003). In addition, pathophysiological data suggest that submucosal UL are distinct clinical entities from other UL. Specifically, abnormal karyotypes have been reported to be less prevalent in submucosal UL than in intramural or subserosal UL (Brosens et al. 1998), and estrogen receptor and progesterone receptor levels were found to be higher in submucosal UL than in subserosal UL, both during the proliferative phase and the secretive phase of the menstrual cycle (Marugo et al. 1989).

Very little is known about the pathophysiology of the diffuse only subtype. The diffuse heterogeneous echo pattern associated with this subtype may result from multiple small focal UL, or from larger UL that lack the usual distinct histological demarcation from the surrounding myometrium. We considered the diffuse heterogeneous echo pattern as a UL subtype because like focal UL, in the NIEHS UFS it is associated with enlargement of the uterus (Baird et al. 2003) and excess bleeding (Wegienka et al. 2003). Adenomyosis also can present as a diffuse heterogeneous echo pattern, but adenomyosis is usually accompanied by UL in uteri > 280g and occurs alone in only a minority of smaller uteri (LevGur 1996).

Current smoking was positively associated with the diffuse only subtype among both African American and Caucasian women (aOR 2.13 95% CI: 1.29, 3.53 for all women combined), but appeared to have little or no association with either submucosal UL or intramural/subserosal UL. The lack of an association between smoking and submucosal or intramural/subserosal UL is consistent with data for clinically diagnosed UL from the Nurses Health Study (Marshal et al. 1998 a) and the Black Women's Health Study (Wise et al. 2004

b). The positive association between smoking and the diffuse only subtype supports our assumption that this ultrasound finding is not a marker for adenomyosis, which has been found to be inversely associated with smoking in a previous study (Parazzini et al. 1997). The associations we see are quite strong (adjusted ORs of 2.0 and 3.0) and the fact that it is seen in two separate groups strengthens the likelihood that this is a real association.

Our findings with regard to pregnancies did not replicate those of Faerstein et al. (2001 a), who reported that parity was negatively associated with "any submucosal UL" but positively associated with "non-submucosal UL" in a clinic-based study population that included 111 women with information on UL location. In contrast, we noted inverse associations for both focal UL subtypes and pregnancies after age 24, in both African American and Caucasian women, after adjusting for age, age at menarche, BMI, physical activity, and current smoking. However it should be noted that we also found that submucosal UL were the subtype with the strongest inverse association with our parity measure.

One possible explanation may be the hypothesized protective effect of postpartum involution of the uterus, which may clear small UL during the remodeling of the myometrial tissue (Baird and Dunson 2003). The stronger negative association between pregnancies and submucosal UL versus intramural/subserosal UL could be due to the expulsion of (especially submucosal) UL during pregnancy. Previously reported inverse associations between parity and UL in general could not be explained by UL-related infertility (Marshall et al. 1998 b) (Baird and Dunson, 2003), and in the present study the associations between pregnancies after age 24 and UL subtypes were very similar after the exclusion of women who reported being infertile after age 25 (data not shown).

The primary strength of our study is the sonogram-based screening for UL among randomly selected premenopausal women irrespective of clinical symptoms. As such women with both symptomatic and asymptomatic UL could be accurately classified according to UL status and subtype. In addition, we were able to estimate subtype-specific associations separately by ethnicity. Consistent associations for most exposures across ethnic groups support the validity of our subtype-specific estimates. A major limitation is the cross-sectional study design, which does not allow for confirmation that exposures to extrinsic risk factors preceded the onset of UL. In addition the Caucasian women in the study tended to be of high socioeconomic status (SES) and low parity and, as such, the finding noted may not be generalizable to US Caucasian women of low SES and/or high parity. Lastly, although overall sample sizes were relatively large, particularly for African American women, we had reduced power to estimate effects for UL subtypes, especially among Caucasians.

In summary, despite possible histopathologic differences, submucosal UL appear to have a very similar risk factor profile to intramural/subserosal UL. In contrast, the diffuse only subtype may have a somewhat different risk factor profile. Smoking was unrelated to focal UL, but it appears to be a strong risk factor for the diffuse only subtype. These findings suggest that future studies of UL etiology should distinguish focal UL from the diffuse only subtype.

REFERENCES

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 Jan;188:100-107.

Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology. 2003 Mar;14:247-250.

Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. Association of physical activity with development of uterine leiomyoma. Am J Epidemiol. 2007 Jan 15;165:157-163.

Brosens I, Deprest J, Dal CP, Van DH. Clinical significance of cytogenetic abnormalities in uterine myomas. Fertil Steril. 1998;69:232-235.

Brosens J, Campo R, Gordts S, Brosens I. Submucous and outer myometrium leiomyomas are two distinct clinical entities. Fertil Steril. 2003 Jun;79:1452-1454.

Faerstein E, Szklo M, Rosenshein N. Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage, reproductive history, body size, and smoking. Am J Epidemiol. 2001 Jan 1;153:1-10.

Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003 Jun;111:1037-1054.

Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol. 2006 Oct;195:955-964.

LevGur M. The enlarged uterus. Relation of uterine size to symptoms and histopathologic findings. J Reprod Med. 1996;41:166-170.

Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, Stampfer MJ, Hunter DJ. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril. 1998;70:432-439.

Marshall LM, Spiegelman D, Manson JE, Goldman MB, Barbieri RL, Stampfer MJ, Willett WC, Hunter DJ. Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. Epidemiology. 1998;9:511-517.

Marugo M, Centonze M, Bernasconi D, Fazzuoli L, Berta S, Giordano G. Estrogen and progesterone receptors in uterine leiomyomas. Acta Obstet Gynecol Scand. 1989;68:731-735.

Parazzini F, Vercellini P, Panazza S, Chatenoud L, Oldani S, Crosignani PG. Risk factors for

adenomyosis. Hum Reprod. 1997;12:1275-1279.

Stewart EA. Uterine fibroids. Lancet. 2001 Jan 27;357:293-298.

Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol. 2001 Jun;44:364-371.

Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, Schectman JM, Hartmann KE. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101:431-437.

Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, Rosenberg L. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology. 2005 May;16:346-354.

Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Hum Reprod. 2004 Aug;19:1746-1754.

Table 4.1. Characteristics of premenopausal women from the NIEHS Uterine Fibroid Study by race and overall.

Characteristic	African American (N=581) No. (%)	Caucasian (N=405) No. (%)	All (N=986) No. (%)
Age (years)			
<40	248 (42.7)	143 (35.3)	391 (39.7)
40-44	194 (33.4)	130 (32.1)	324 (32.9)
45+	139 (23.9)	132 (32.6)	271 (27.5)
Age at Menarche			
<11	61 (10.6)	18 (4.5)	79 (8.1)
11	93 (16.1)	59 (14.6)	152 (15.5)
12	160 (27.7)	111 (27.5)	271 (27.6)
13	141 (24.4)	138 (34.2)	279 (28.4)
14	54 (9.3)	43 (10.7)	97 (9.9)
>14	69 (11.9)	34 (8.4)	103 (10.5)
Missing	3	2	5
Any Pregnancies			
No	297 (51.1)	256 (63.2)	553 (56.1)
Yes	284 (48.9)	149 (36.8)	433 (43.9)
Body Mass Index			
<25	148 (25.5)	234 (57.8)	382 (38.8)
25-29.99	180 (31.0)	98 (24.2)	278 (28.2)
30-34.99	115 (19.8)	37 (9.1)	152 (15.4)
35+	137 (23.6)	36 (8.9)	173 (17.6)
Missing	1	0	1
Physical Activity*			
Low/Medium	399 (69.2)	243 (60.2)	642 (65.4)
High/Very	178 (30.9)	161 (39.9)	339 (34.6)
Missing	4	1	5
Current Smoking			
No	412 (70.9)	372 (91.9)	784 (79.5)
Yes	169 (29.1)	33 (8.2)	202 (20.5)
Location of UL			
No UL	162 (27.9)	202 (49.9)	364 (36.9)
Diffuse only	78 (13.4)	40 (9.9)	118 (12.0)
Submucosal	93 (16.0)	40 (9.9)	133 (13.5)
	248 (42.7)	123 (30.8)	371 (37.6)

* Physical activity without chores (indexed to estimated hours/week of vigorous activity): low (<1.85), medium (1.85-4.14), high (4.15-6.55), very high (>6.55).

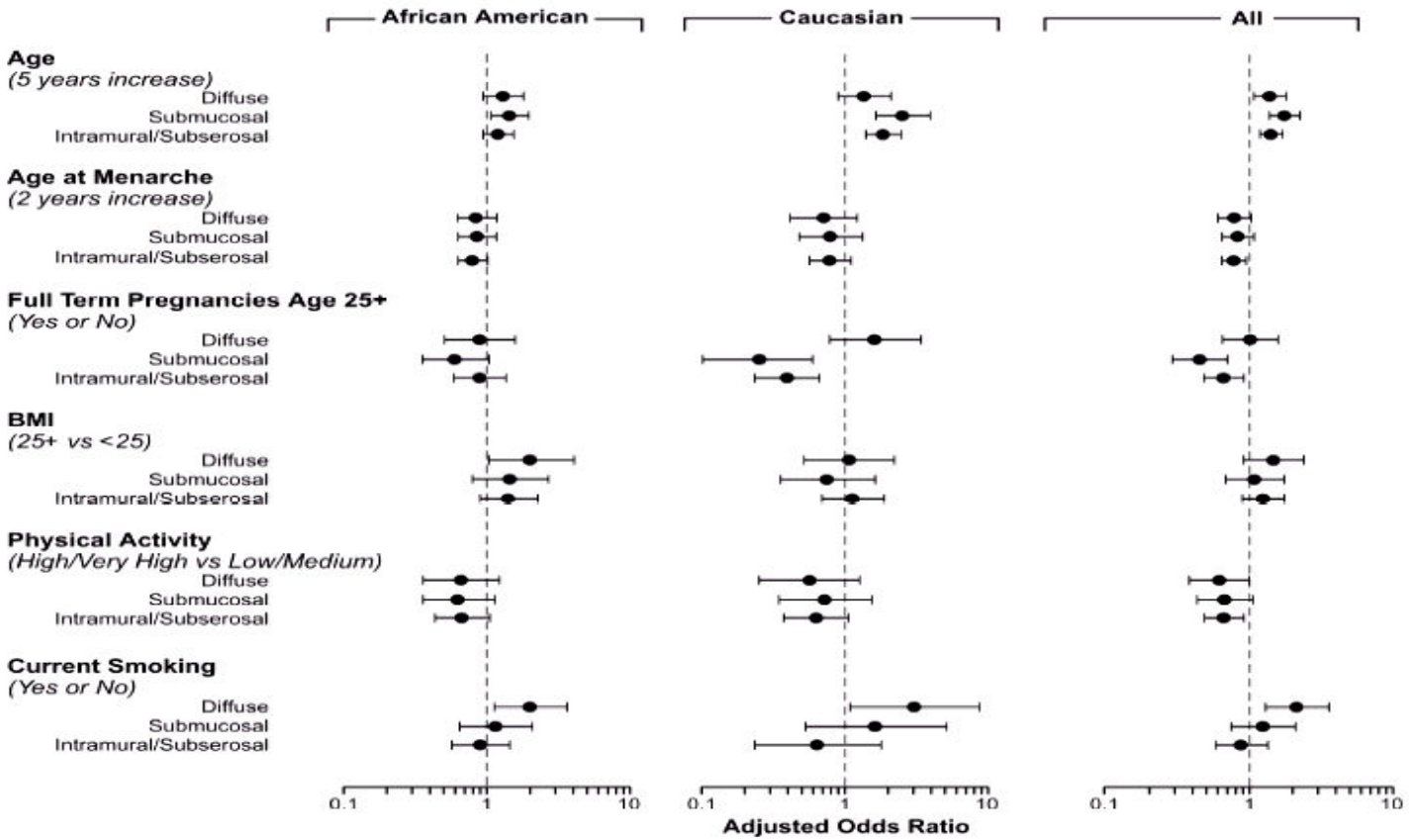

FIGURE 4.1. Estimated adjusted odds ratios for the associations of uterine leiomyomata subtypes with age, age at menarche, full term pregnancies after age 24, body mass index (BMI; kg/m^2), physical activity, and current cigarette smoking among African American, Caucasian, and all premenopausal women in the NIEHS Uterine Fibroid Study. For the race-specific analyses the estimated odds ratios for each risk factor are adjusted for the other five risk factors; for the overall analysis they are adjusted for the other five risk factors and race. Horizontal lines are the corresponding 95% confidence intervals.

Table 4.2. Estimated adjusted odds ratios for the associations of UL subtypes with age, age at menarche, any full term pregnancies after age 24, body mass index (BMI; kg/m^2), physical activity, and current cigarette smoking among African American, Caucasian, and all premenopausal women in the NIEHS Uterine Fibroid Study. For the race-specific analyses the estimated odds ratios for each risk factor are adjusted for the other five risk factors; for the overall analysis they are adjusted for the other five risk factors and race.

	African American			Caucasian			All	
	N*	**aOR**	**95% CI**	**N***	**aOR**	**95% CI**	**OR**	**95% CI**
Age (5 years increase)								
Diffuse only	-	1.28	0.93 , 1.77	-	1.34	0.89 , 2.04	1.38	1.07 , 1.78
Submucosal	-	1.42	1.05 , 1.92	-	2.49	1.62 , 3.83	1.75	1.37 , 2.23
Intramural/Subserosal	-	1.18	0.94 , 1.50	-	1.82	1.37 , 2.41	1.40	1.18 , 1.68
Age at Menarche (2 years increase)								
Diffuse only	-	0.83	0.61 , 1.13	-	0.70	0.41 , 1.18	0.78	0.60 , 1.02
Submucosal	-	0.84	0.62 , 1.13	-	0.78	0.47 , 1.30	0.82	0.64 , 1.06
Intramural/Subserosal	-	0.78	0.62 , 0.98	-	0.77	0.55 , 1.07	0.77	0.64 , 0.94
Fullterm Pregnancies Age 25+ (Yes vs. No)								
No UL	86:76	1.00		85:117	1.00		1.00	
Diffuse only	39:39	0.88	0.50 , 1.54	23:17	1.58	0.76 , 3.28	1.01	0.65 , 1.57
Submucosal	37:56	0.59	0.35 , 1.01	8:32	0.25	0.10 , 0.58	0.45	0.29 , 0.69
Intramural/Subserosal	122:126	0.88	0.58 , 1.32	33:90	0.39	0.23 , 0.65	0.66	0.48 , 0.90
BMI (kg/m^2) (25+ vs. <25)								
No UL	108:54	1.00		80:122	1.00		1.00	
Diffuse only	63:15	1.99	1.01 , 3.94	18:22	1.05	0.51 , 2.15	1.46	0.91 , 2.37
Submucosal	71:21	1.43	0.78 , 2.62	15:25	0.74	0.35 , 1.58	1.08	0.69 , 1.71
Intramural/Subserosal	190:58	1.39	0.88 , 2.20	58:65	1.11	0.68 , 1.82	1.24	0.89 , 1.72

Physical Activity (High/Very High vs. Low/Medium)								
No UL	62:99	1.00		91:110	1.00		1.00	
Diffuse only	22:56	0.65	0.35 , 1.19	11:29	0.56	0.25 , 1.23	0.62	0.38 , 0.99
Submucosal	25:67	0.62	0.35 , 1.11	16:24	0.71	0.34 , 1.50	0.67	0.43 , 1.05
Intramural/Subserosal	69:177	0.66	0.43 , 1.02	43:80	0.62	0.37 , 1.03	0.66	0.48 , 0.91
Current Smoking (Yes vs. No)								
No UL	46:116	1.00		14:188	1.00		1.00	
Diffuse only	33:45	1.97	1.11 , 3.51	7:33	3.00	1.07 , 8.38	2.13	1.29 , 3.53
Submucosal	28:65	1.13	0.64 , 2.01	5:35	1.60	0.52 , 4.98	1.24	0.74 , 2.07
Intramural/Subserosal	62:186	0.89	0.56 , 1.40	7:116	0.63	0.23 , 1.74	0.87	0.58 , 1.32

*** N** represents counts for Exposed: Unexposed

Table 4.3. P-values from tests of equal associations* across the three UL subtypes for each of the six risk factor of interest, among African American, Caucasian, and all premenopausal women in the NIEHS Uterine Fibroid Study.

	African-American	Caucasian	All
Age	0.438	0.084	0.162
Age at Menarche	0.849	0.939	0.900
Any Pregnancy 25+	0.265	**< 0.001**	**0.010**
BMI	0.564	0.588	0.589
Current Smoking	**0.014**	**0.036**	**0.002**
Physical Activity	0.975	0.886	0.951

* Wald chi-squared tests with 2 degrees of freedom to test the equality of three adjusted odds ratio, one for the association with each UL subtype. For the race-specific analyses the polytomous logistic regression models includes the six risk factors; for the overall analysis the polytomous logistic regression model includes race as well. P-values < 0.05 are bolded.

CHAPTER V

PAPER 2: SELF-REPORTED URINARY SYMPTOMS ASSOCIATED WITH UTERINE LEIOMYOMATA

Abstract

OBJECTIVE: To investigate the association between uterine leiomyomata (UL) and self-reported stress urinary incontinence (SUI) in premenopausal women.

METHODS: This study used baseline (1996-1999) and follow-up (2001-2002) data from 798 premenopausal participants (446 African-American and 352 Caucasian) in the National Institute of Environmental Health Sciences Uterine Fibroid Study. At follow-up, participants were asked about symptoms during a 12-month reference period, and women were classified as having SUI if they reported any urine leak when they coughed or sneezed. UL status was characterized at baseline using transabdominal and transvaginal ultrasound. The UL risk factors considered were: presence of any UL, size of the largest UL, presence of a large (≥ 4cm) anterior UL in a non-retroverted uterus, presence of a medium/large (≥ 2cm) anterior UL in a non-retroverted uterus, and uterine size. Linear risk models were used to estimate adjusted prevalence differences (aPD) and 95% confidence intervals (CI) controlling for age, ethnicity, body mass index (BMI), and the number of deliveries. In addition, ethnicity and parity were evaluated as effect measure modifiers.

RESULTS: About half (51%) of study participants reported SUI during the reference period. Compared with women without any UL, SUI prevalence was higher among women

with any UL (aPD=6.7 95% CI: -0.5, 13.7), and with a medium or large UL (aPD=9.0 95% CI: 0.3, 17.4 and 8.6 95% CI: -1.4, 18.6, respectively). Anterior location was not associated with further increase in prevalence. Women with very large uterine volume (≥ 206.5 cm^3) reported more SUI than those with small uterine volume (<91.4 cm^3, aPD=9.1 95% CI: -1.5, 19.5), but SUI was not associated with intermediate categories of uterine volume. There was no clear evidence of PD modification by ethnicity or parity.

CONCLUSIONS: We found increases in SUI prevalence of about 7% to 9% with UL. The associations were not as strong as for established risk factors such as parity and obesity, which were associated with increased prevalences ranging from 13% to 22%. However, for a common outcome like SUI even this smaller increase in prevalence is important. Contrary to expectations, an anteriorly located UL was not associated with higher prevalence than UL in other locations. Uterine volume above the 83rd percentile for the population (>206.5 cm^3), which may reflect the overall burden of UL better than the size of the largest UL, also was positively associated with SUI. Overall, these findings suggest that treatment for larger UL might enhance SUI treatment in some women.

Introduction

Urinary incontinence is one of the most common types of lower urinary tract dysfunction, affecting about a third of adult women in the United States (DuBeau 2001). The annual direct cost of urinary incontinence for women in the US is estimated as $12.4 billion (in 1995 dollars) (Wilson et al. 2001).

Stress urinary incontinence (SUI), the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing (Abrams et al. 2002), is the most common type

of urinary incontinence in women, with about half of women with urinary incontinence suffering from SUI (Hampel et al. 1997). SUI accounts for 85% of treatment expenditures for urinary incontinence for women (Wilson et al. 2001), and also may have a substantial negative impact on the quality of life (Contreras-Ortiz 2004).

Established risk factors for self-reported SUI symptoms include age, ethnicity, body mass index (BMI), parity, and mode of delivery. In particular several epidemiological studies have identified older age (Goldberg et al. 2005), Caucasian race (vs. African-American) (Jackson et al. 2004, Thom et al. 2006), high BMI (Mommsen and Foldspang 1994, Hojberg et al. 1999, Jackson et al. 2004), parity (Foldspang et al. 1992), and history of vaginal deliveries (Hojberg et al. 1999, Han et al. 2005) as risk factors for self-reported SUI.

Uterine enlargement due to the presence of uterine leiomyomata (UL), in particular large UL in the anterior lower uterus, may cause urinary symptoms by extrinsically compressing the urinary bladder (Haney 2000). In particular, laughing, coughing, or sneezing, may displace UL against the bladder and cause involuntary loss of urine (i.e. SUI). It has been hypothesized that UL may be associated with SUI (Stovall 2001, Altman et al. 2003, Sampselle et al. 2002, Nygaard and Heit 2004). There is also a case report of a pedunculated UL causing acute SUI (Isherwood et Rane 1999). However, an epidemiological study investigating the association of parity and route of delivery with self-reported SUI during the previous month, found no association between UL (as the primary indication for hysterectomy) and SUI (Handa et al. 2004). The authors compared the prevalence of SUI between women who had hysterectomies due to UL and women who had hysterectomies due to other causes. UL was not the main risk factor under investigation, and only an unadjusted

OR was reported for the association between UL and SUI. It should be noted that the study used a highly selective sample, not representative of women with UL or women with SUI.

No population-based observational studies have directly assessed the association between UL and self-reported SUI. Therefore, the objective of this study was to investigate the association between SUI and UL overall, and between SUI and UL characteristics, among 446 African-American and 352 Caucasian premenopausal women who participated in the first follow-up interview of the National Institute of Environmental Health Science's (NIEHS) Uterine Fibroid Study.

Methods

The NIEHS Uterine Fibroid Study (UFS), which was approved by Human Subject Review Boards at the NIEHS and George Washington University, was designed to measure the prevalence of UL, identify risk factors for UL, and evaluate UL-related symptoms among African American and Caucasian women. Enrollment occurred between 1996 and 1999 at which time participants were screened for UL and baseline data were collected using a mail questionnaire that took about 30 minutes to complete, and a telephone interview, which lasted one hour. Premenopausal participants were followed-up in 2001-2002 using a computer-assisted telephone interview.

Study Participants: The UFS enrolled women aged 35 to 49 years old who were selected randomly from a computerized list of health plan members at a Washington, DC site. In addition to age and health plan membership requirements, eligible women had to be able to complete the UFS study interview in English. Of the 2,102 women screened for enrollment, 316 (15%) were ineligible, primarily because they did not obtain care at the

Washington, DC health plan site. Of the 1,786 eligible women, 335 (19%) refused to participate, and 24 (1%) were lost to contact prior to data collection. In total, 1,430 women, constituting 80% of the eligible women, participated in the baseline phase of the UFS.

Out of the 1,430 baseline participants, 1,144 were premenopausal African-American or Caucasian women, and out of these 913 participated in the first follow-up of the NIEHS UFS. Women were excluded from the current study if they were missing data on SUI (n = 4) or on selected UL characteristics (n = 92). In addition, women who were pregnant during the 12-month reference interval for self-reported history of SUI (n =14) and women for whom the age at reference was unknown (n = 5) were also excluded from the current study. The final population included 798 premenopausal women, 446 African-American and 352 Caucasian.

Determination of UL Status: During the baseline telephone interview, women were asked: "Have you ever been told by a doctor or other health professional that you have uterine fibroid tumors or a leiomyoma, a benign tumor of the uterus or womb?" Women who answered affirmatively and did not report a subsequent misdiagnosis in response to questions about diagnostic or follow-up examinations, UL treatment, or UL persistence, were classified as having a previous diagnosis of UL. For most women UL was identified or confirmed based on a pelvic ultrasound examination conducted for the study at the primary care site. Women who were previously diagnosed with UL and had an ultrasound during the previous five years, or were not diagnosed with UL and had an ultrasound during the previous two years, had those sonograms used instead of a study sonogram.

Study ultrasound examinations included both transabdominal and transvaginal examinations to facilitate identification of UL in the upper uterus. Both examinations were

performed by sonographers certified by the American Registry of Diagnostic Medical Sonographers, under the supervision of a radiologist with fellowship training in sonography. A single radiologist reviewed all questionable sonograms. Sonographers filled out a study-specific data collection form that included data on uterine size, uterine shape, the presence of diffuse heterogeneous echo pattern, number of focal UL, the size and location of the two largest UL (if at least 2cm in diameter), and the size of the three largest submucosal UL.

UL status was classified according to 1) the presence of any UL (any UL vs. no UL), 2) the size of the largest UL (no UL, small (< 2cm) UL, medium (2-4cm) UL, large (≥ 4cm) UL), 3) the presence of a large (≥ 4cm) anterior UL in a non-retroverted uterus (no UL, large (≥ 4cm) anterior UL in non-retroverted uterus, other UL), or 4) the presence of a medium/large (≥ 2cm) anterior UL in a non-retroverted uterus (no UL, medium/large (≥ 2cm) anterior UL in non-retroverted uterus, other UL). In addition, 774 women were classified according to overall uterine volume (small (lowest 33% of overall uterine volume distribution), medium (middle 33%), large (those in 67th to 83rd percentile), and very large (those above the 83rd percentile)), with uterine volume calculated using the prolate ellipsoid formula (0.52 x length x width x anterior/posterior diameter). The actual cut points used to define the four categories of uterine size were: 91.4 cm^3 (the 33rd percentile), 147.8 cm^3 (the 66th percentile), and 206.5 cm3 (the 83rd percentile).

For the previous definitions the "no UL" category included women who had neither focal UL nor a diffuse heterogeneous echo pattern present. The later may result from multiple small focal UL, or from larger UL that lack the usual distinct histological demarcation from the surrounding myometrium. We considered the diffuse heterogeneous echo pattern as an indicator of UL being present because like focal UL, in the NIEHS UFS it

is associated with enlargement of the uterus (Baird et al. 2003) and excess bleeding (Wegienka et al. 2003). Adenomyosis also can present as a diffuse heterogeneous echo pattern, but adenomyosis is usually accompanied by UL in uteri > 280g and occurs alone in only a minority of smaller uteri (LevGur 1996). For the 87 women who had a diffuse heterogeneous echopattern and no detectable focal UL we assigned a UL size based on their uterine volume.

SUI Determination: Data collected at the follow-up during the computer-assisted telephone interview included self-reported history of SUI, which was classified as positive if women reported that they ever had urine leak when they coughed or sneezed during the 12 month interval prior to a reference date determined by UL treatment and menstrual history. The reference date for women who had had UL treated by myomectomy, hystereoscopic resection, uterine artery embolization, or hysterectomy was the date of the procedure if they were still menstruating, or was the date of their last period if they had stopped menstruating prior to the treatment procedure. The reference date for women who did not undergo any of the procedures listed above was the date of their follow-up interview if they were still menstruating, or the date of their last period if they did not report a period in the last two months.

Data Analysis: Potential confounders selected based on a review of the literature regarding risk factors for UL and SUI included age at the reference date (continuous or categorized as <40, [40,45), [45,50), 50+), ethnicity (African-American, Caucasian), BMI at baseline (kg/m^2, categorized as <25, [25,30), [30,35), 35+), and the number of deliveries prior to the reference date (categorical, 0, 1, 2, 3+). A composite variable involving the number and the type of deliveries (none, only C-section deliveries, 1 vaginal delivery, 2

vaginal deliveries, 3+ vaginal deliveries) was also evaluated as a potential confounder, but was not used since results were comparable with those adjusted for the number of deliveries.

Univariate analyses were performed to describe the distributions of exposures and outcomes, and assess missing data. Given the prevalence of the outcome under study (about 50% of the participants have reported SUI), odds ratios are an overestimate for the relative risk. Therefore, we used linear risk models to estimate prevalence differences (PD) and corresponding 95% confidence intervals (CI) (Spiegelman and Hertzmark, 2005). Separate linear risk models were used to evaluate the association between each of the five variables of interest and self-reported SUI. We estimated crude, ethnicity-adjusted, and fully-adjusted PDs with 95% CIs, with the fully-adjusted estimates from linear risk models that included age at reference (continuous), ethnicity, BMI, and number of deliveries. All model estimates were evaluated to confirm that predicted prevalences were between 0 and 1.

Ethnicity was evaluated as a potential effect modifier since African American women are at increased risk of UL but at decreased risk of SUI compared with Caucasians. In addition we evaluated effect modification by parity (nulliparous vs. parous) as pregnancy loosens the pelvic floor. Formal evaluation of effect modification by ethnicity and parity was performed using likelihood ratio tests ($\alpha = 0.10$). All analyses were performed using the SAS software package (SAS v.9.1; SAS Institute, Inc., Cary, North Carolina).

Results

Over half of study participants were African-American, and about a third reported being nulliparous (Table 5.1). Most women were age 40-49 on the reference date (mean (±SD) 45.8 (±4.0) years), and 60% were overweight or obese (mean (±SD) 28.4 (±7.5)

km/m^2). The average time from the ultrasound examination to the reference data was about 4 years (mean (±SD) 3.9 (±2.0) years). Overall, 393 of 798 (51%) of study participants reported SUI during the reference period. Consistent with the literature, African-American women reported less SUI than Caucasian women (43% versus 57%), and there was a general tendency for the prevalence of SUI to increase with age, BMI, and number of deliveries. Sixty-three % of participants had at least one UL (499 of 798), and the prevalence of SUI was increased among women with UL (51%) relative to women without UL (47%). The adjusted prevalence difference (aPD) associated with UL was 6.7 with 95% CI: -0.5, 13.7.

Forty-five % of participants had had at least one UL that was 2cm or larger (Table 5.2). Relatively few women had an anterior UL in a non-retroverted uterus that was ≥ 4cm or ≥ 2cm (4% and 15% respectively). The prevalence of SUI was similar for women with no UL and for those with UL < 2cm, but was increased among women with UL 2-4 cm (aPD=9.0 95% CI: 0.3, 17.4) and UL 4cm or larger (aPD=8.6 95% CI: -1.4, 18.6). Contrary to expectations, the association between UL and SUI appeared to be weaker for large (≥ 4cm) anterior UL in a non-retroverted uterus (aPD=2.8 95% CI: -13.4, 19.2) then for other UL (aPD=7.0 95% CI: -0.3, 14.1); however, estimates were imprecise due to the small number of observations in the former group. The association between the presence of anterior UL 2cm or larger in a non-retroverted uterus and SUI (aPD=8.6 95% CI: -1.6, 18.6) was similar to the association estimated for other UL and SUI (aPD=6.1 95% CI: -1.5, 13.5).

The prevalence of SUI among women with a very large uterine volume (> 206.5 cm^3) was increased relative to women with a small uterine volume (≤ 91.4 cm^3) (aPD=9.1 95% CI: -1.5, 19.5); however, SUI was not positively associated with “medium” or “large” uterine volume.

The increase in SUI prevalence associated with medium size (2-4 cm) UL was the only statistically significant finding. Because ethnicity is a very strong risk factor for both SUI and UL, Table 5.1 and Table 5.2 contain crude, ethnicity-adjusted, as well as fully-adjusted PDs with and 95% CIs. There was no evidence that the association between UL presence and SUI differed by race ($p = 0.637$) or parity ($p = 0.999$). For example the race-specific associations between UL presence and SUI were similar, aPD=8.3 95% CI: -1.4, 18.0 for African-Americans and aPD=4.9 95% CI: -5.3, 15.1 for Caucasians. In addition, there was no evidence of PD modification by ethnicity or parity when UL was classified according to size or position, or of modification of the association between uterine volume and SUI (all likelihood ratio test p-values > 0.10). The results did not change qualitatively when the 87 women who had a diffuse heterogeneous echopattern and no detectable focal UL were excluded.

Discussion

Although several papers have hypothesized that UL may be associated with SUI (Stovall 2001, Altman et al. 2003, Sampselle et al. 2002, Nygaard and Heit 2004), this is the first population-based epidemiological study to systematically evaluate the association between UL characteristics and presence of self-reported SUI. In addition to the presence or absence of any UL, we evaluated the size of the largest UL, UL location, and overall uterine volume, since these characteristics may affect SUI by increasing pressure exerted on the bladder.

Almost half of the study population reported symptoms of SUI during the reference interval, but the prevalence of SUI was about 7% higher among women with UL compared

with women without UL after adjusting for age, ethnicity, BMI, and number of deliveries. Relative to women without UL, the prevalence of SUI was about 9% higher among women with UL that were 2cm or larger, and among women with a very large uterine volume. However, an anterior UL of at least 4 cm in a non-retroverted uterus, which we hypothesized would be most likely to exert pressure on the bladder, was not more strongly associated with SUI than other UL. In addition, we did not see evidence that associations between UL and SUI were modified by race or parity.

The association between the presence of UL and urinary incontinence has been only indirectly investigated in previous studies. A cross–sectional study involving 1,293 women scheduled for hysterectomy evaluated the association between self-reported SUI during the previous month and UL as the primary indication for hysterectomy (versus other indications for hysterectomy) (Handa et al. 2004). Women with UL as the primary indication were no more likely to report SUI as women with other indications for hysterectomy (such as noninfectious conditions, cancer and premalignant conditions, adnexal conditions, and infections). However for the reasons provided in the introduction part this study cannot be used as evidence against an association between UL and SUI.

Sampselle et al. (2002) studied 3,302 women aged 42 to 52 years old that were enrolled in the Study of Women's Health Across the Nation cohort, a multiethnic longitudinal study of the natural history of menopausal transition (47% Caucasian, 28% African-American). Women were classified as having UL if they reported that a health care provider had ever told them that they had the condition. The authors estimated associations between ethnicity and incontinence according to UL status, but did not estimate the association between UL and incontinence specifically. Among women without UL, African-

American women were less likely than Caucasian women to report urinary incontinence (aOR = 0.31 95% CI: 0.23, 0.40 adjusted for age, menopausal status, BMI, diabetes, and parity). However, among women with UL, African-American women were more likely than Caucasian women to report urinary incontinence (aOR = 1.81 95% CI: 1.22, 2.71). To explain their finding the authors speculated that the propensity of African-American women to develop larger UL resulted in an increased prevalence of SUI, and subsequently an increased prevalence of urinary incontinence.

There have been few studies that have looked on the effect of hysterectomy on SUI symptoms. In a prospective study the SUI prevalence dropped from 36% before surgery to 19% six months after surgery (El-Toukhy et al. 2004). Two randomized clinical trials have also found reductions in SUI after hysterectomy (Thakar et al. 2002, Gimbel et al. 2005). In the first clinical trial the reduction in SUI was not associated with UL presence, while in the second the SUI reduction was attributed to the removal of uteri with large UL. We found no literature on the effect of myomectomy or uterine artery embolization on SUI, studies that would more directly address the efficacy of removal of UL for treating SUI.

A strength of our study is that UL status was based on screening a randomly selected sample, so women with both symptomatic and asymptomatic UL could be accurately classified. The ultrasound data also allowed us to characterize the size and location of UL. In addition, our outcome measure was restricted to SUI, versus self-reported urinary incontinence of any type as in Sampselle et al. (2002). However, we could not confirm that UL preceded the onset of SUI, and the number of women with large (≥ 4cm) anterior UL in a non-retroverted uterus was small (n=34).

In summary, we found an increase in SUI prevalence of about 7% associated with the presence of UL, with slightly larger increases in prevalence associated with larger UL and large uterine volume. These findings are consistent with expectations regarding associations between UL and SUI, and suggest that the effective treatment of SUI may require treatment for larger UL in some cases.

REFERENCES

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van KP, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol. 2002 Jul;187:116-126.

Altman D, Lopez A, Falconer C, Zetterstrom J. The impact of hysterectomy on lower urinary tract symptoms. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Dec;14:418-423.

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 Jan;188:100-107.

Contreras-Ortiz O. Stress urinary incontinence in the gynecological practice. Int J Gynaecol Obstet. 2004 Jul;86 Suppl 1:S6-16.

DuBeau CE. Urinary incontinence management: new questions from old assumptions. J Am Geriatr Soc. 2001 Jun;49:829-830.

El-Toukhy TA, Hefni M, Davies A, Mahadevan S. The effect of different types of hysterectomy on urinary and sexual functions: a prospective study. J Obstet Gynaecol. 2004 Jun;24:420-425.

Foldspang A, Mommsen S, Lam GW, Elving L. Parity as a correlate of adult female urinary incontinence prevalence. J Epidemiol Community Health. 1992;46:595-600.

Gimbel H, Zobbe V, Andersen BJ, Sorensen HC, Toftager-Larsen K, Sidenius K, Moller N, Madsen EM, Vejtorp M, Clausen H, Rosgaard A, Villumsen J, Gluud C, Ottesen BS, Tabor A. Lower urinary tract symptoms after total and subtotal hysterectomy: results of a randomized controlled trial. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Jul-Aug;16:257-262.

Goldberg RP, Abramov Y, Botros S, Miller JJ, Gandhi S, Nickolov A, Sherman W, Sand PK. Delivery mode is a major environmental determinant of stress urinary incontinence: results of the Evanston-Northwestern Twin Sisters Study. Am J Obstet Gynecol. 2005 Dec;193:2149-2153.

Hampel C, Wienhold D, Benken N, Eggersmann C, Thuroff JW. Prevalence and natural history of female incontinence. Eur Urol. 1997 32 Suppl 2:3-12.

Han MO, Lee NY, Park HS. Abdominal obesity is associated with stress urinary incontinence in Korean women. Int Urogynecol J Pelvic Floor Dysfunct. 2005 Jan;17:35-39.

Handa VL, Harvey L, Fox HE, Kjerulff KH. Parity and route of delivery: does cesarean

delivery reduce bladder symptoms later in life? Am J Obstet Gynecol. 2004 Aug;191:463-469.

Haney AF. Clinical decision making regarding leiomyomata: what we need in the next millenium. Environ Health Perspect. 2000 Oct;108 Suppl 5:835-839.

Hojberg KE, Salvig JD, Winslow NA, Lose G, Secher NJ. Urinary incontinence: prevalence and risk factors at 16 weeks of gestation. Br J Obstet Gynaecol. 1999;106:842-850.

Isherwood PJ, Rane A. Pedunculated uterine leiomyoma causing acute urinary stress incontinence. J Obstet Gynaecol. 1999;19:440-441.

Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, Simonsick EM, Brown JS. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol. 2004 Aug;104:301-307.

LevGur M. The enlarged uterus. Relation of uterine size to symptoms and histopathologic findings. J Reprod Med. 1996;41:166-170.

Mommsen S, Foldspang A. Body mass index and adult female urinary incontinence. World J Urol. 1994;12:319-322.

Nygaard IE, Heit M. Stress urinary incontinence. Obstet Gynecol. 2004 Sep;104:607-620.

Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol. 2002 Dec;100:1230-1238.

Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol. 2005 Aug 1;162:199-200.

Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol. 2001 Jun;44:364-371.

Thakar R, Ayers S, Clarkson P, Stanton S, Manyonda I. Outcomes after total versus subtotal abdominal hysterectomy. N Engl J Med. 2002 Oct 24;347:1318-1325.

Thom DH, van dK, Ragins AI, Wassel-Fyr C, Vittinghof E, Subak LL, Brown JS. Differences in prevalence of urinary incontinence by race/ethnicity. J Urol. 2006 Jan;175:259-264.

Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, Schectman JM, Hartmann KE. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101:431-437.

Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary

incontinence. Obstet Gynecol. 2001 Sep;98:398-406.

Table 5.1. UL presence and confounder variables with corresponding SUI prevalences, unadjusted, ethnicity-adjusted, and fully-adjusted* prevalence differences (PD) for the 798 premenopausal women included in the study.

	N	Prevalence of SUI %	Unadjusted PD	Unadjusted 95% CI	Ethnicity Adjusted PD	Ethnicity Adjusted 95%CI	Fully Adjusted PD	Fully Adjusted 95% CI
UL Presence								
No (ref)	299	46.5	0		0		0	
Yes	499	50.9	4.4	-2.8, 11.5	8.6	1.3, 15.8	6.7	-0.5, 13.7
Ethnicity								
African-American (ref)	446	43.1	0		-		0	
Caucasian	352	57.1	14.1	7.1, 20.9	-	-	26.4	18.6, 33.6
BMI (kg/m^2)								
<25 (ref)	325	42.8	0		0		0	
[25, 30)	214	53.3	10.5	1.9, 19.0	15.1	6.5, 23.4	13.0	4.7, 21.3
[30, 35)	119	51.3	8.5	-2.0, 18.8	16.7	5.8, 27.3	14.5	3.8, 25.0
35+	140	56.4	13.7	3.8, 23.3	21.0	11.1, 30.5	21.9	11.9, 31.4
Number of Deliveries								
0 (ref)	294	44.2	0		0		0	
1	142	48.6	4.4	-5.6, 14.3	12.1	1.8, 22.2	13.2	3.1, 23.2
2	238	54.6	10.4	1.9, 18.8	16.4	7.8, 24.8	16.5	8.0, 24.8
3+	124	51.6	7.4	-3.1, 17.8	17.3	6.5, 27.8	16.6	5.8, 27.0
Age at Reference Date**								
Per 5 years increase	-	-	5.6	1.3, 9.9	4.9	0.6, 9.1	2.5	-1.7, 6.8

* Adjusted for all other variables in a linear risk model that included UL presence, age at reference date, ethnicity, BMI, and number of deliveries.
**The reference date for women who had had UL treated by myomectomy, hystereoscopic resection, uterine artery embolization, or hysterectomy was the date of the procedure if they were still menstruating, or was the date of their last period if they had stopped menstruating prior to the treatment procedure. The reference date for women who did not undergo any of the procedures listed above was the date of their follow-up interview if they were still menstruating, or the date of their last period if they did not report a period in the last two months.

Table 5.2. UL characteristics with corresponding SUI prevalences, unadjusted, ethnicity-adjusted, and fully-adjusted* prevalence differences (PD) for the 798 premenopausal women included in the study.

	N	Prevalence of SUI %	Unadjusted PD	Unadjusted 95% CI	Ethnicity Adjusted PD	Ethnicity Adjusted 95%CI	Fully Adjusted PD	Fully Adjusted 95% CI
UL Size								
No UL (ref)	299	46.5	0		0		0	
< 2 cm	140	47.1	0.7	-9.3, 10.7	3.4	-6.4, 13.3	1.5	-8.1, 11.3
2 - 4 cm	223	52.9	6.4	-2.2, 15.0	11.1	2.4, 19.6	9.0	0.3, 17.4
4+ cm	136	51.5	5.0	-5.1, 15.0	10.5	0.1, 20.8	8.6	-1.4, 18.6
Anterior UL 4+cm								
No (ref)	299	46.5	0		0		0	
Yes	34	47.1	0.6	-16.6, 18.1	5.2	-12.1, 22.7	2.8	-13.4, 19.2
Other UL	465	51.2	4.7	-2.6, 11.9	8.9	1.5, 16.2	7.0	-0.3, 14.1
Anterior UL 2+cm								
No (ref)	299	46.5	0		0		0	
Yes	122	51.6	5.2	-5.4, 15.6	10.2	-0.3, 20.6	8.6	-1.6, 18.6
Other UL	377	50.7	4.2	-3.4, 11.7	8.1	0.4, 15.7	6.1	-1.5, 13.5
Uterine Size**								
Small (ref)	255	46.7	0		0		0	
Medium	256	46.5	-0.2	-8.8, 8.5	1.4	-7.1, 9.8	-3.7	-12.3, 4.9
Large	132	48.5	1.8	-8.6, 12.3	5.7	-4.9, 16.3	-0.9	-11.5, 9.9
Very Large	131	57.3	10.6	0.1, 20.9	16.7	6.1, 26.9	9.1	-1.5, 19.5

* Adjusted for all confounders: age at reference date, ethnicity, BMI, number of deliveries. The reference date for women who had had UL treated by myomectomy, hystereoscopic resection, uterine artery embolization, or hysterectomy was the date of the procedure if they were still menstruating, or was the date of their last period if they had stopped menstruating prior to the treatment procedure. The reference date for women who did not undergo any of the procedures listed above was the date of their follow-up interview if they were still menstruating, or the date of their last period if they did not report a period in the last two months.

**The cut points used to define the four categories of uterine size are the 33rd percentile (91.4 cm^3), the 66th percentile (147.8cm^3), and the 83rd percentile (206.5 cm^3) of the overall uterine volume distribution.

CHAPTER VI

CONCLUSIONS

Introduction

The common idea behind the two epidemiological studies described in this dissertation was to move research forward from studies of uterine leiomyomata (UL) as a single entity to a more detailed characterization of UL (involving position within the myometrium, size of the largest UL, etc.). In the first study we compared associations with six putative risk factors among three UL subtypes defined by location within the myometrium (submucosal UL, intramural/subserosal UL, and diffuse only). In the second study we investigated UL characteristics as risk factors for self-reported stress urinary incontinence (SUI). It should be noted that in the first paper UL subtype was the outcome, and in the second paper the UL characteristics were the risk factors of interest.

Although UL are the most prevalent tumors among women in the United States (Flake et al. 2003) and there is evidence of histopathologic differences among UL subtypes (Marugo et al. 1989, Brosens et al. 1998), no study to date has systematically investigated risk factor profiles of individual UL subtypes. Similarly, although it has been hypothesized that uterine enlargement due to large anterior UL may cause SUI (Stovall 2001, Sampselle et al. 2002) no population-based epidemiological studies have assessed the association between UL characteristics and SUI.

Both studies used data from the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study (UFS), a study designed to measure the prevalence of UL,

identify risk factors for UL, and evaluate UL-related symptoms among African-American and Caucasian women. The first study used baseline data (collected between 1996 and 1999), while the second study used UFS baseline and follow-up data (collected between 2001 and 2002). Both studies took full advantage of the detailed data obtained from ultrasound examinations (both transabdominal and transvaginal) performed as part of the baseline assessment. The follow-up data examination included self-reported history of SUI during the 12-month period prior to a reference date determined by UL treatment or change in menopausal status.

Summary of Results

For both African-American and Caucasian premenopausal women we found similar associations of four of the risk factors considered (age at ultrasound examination, age at menarche, body mass index, and current physical activity) with the three UL subtypes. For both ethnic groups the inverse association of having any full-term pregnancies after age 24 with the submucosal UL subtype seemed to be stronger than its associations with the intramural/subserosal UL subtype and the diffuse only subtype. There was also a positive association of current smoking with the diffuse UL subtype, in contrast to no associations of current smoking with the two focal UL subtypes, for both African-Americans and Caucasians.

Compared with women with no UL, we found an estimated increase in the prevalence of SUI of 7% associated with any UL, with slightly larger increases (about 9%) among women with medium (2-4 cm) or large (4+ cm) UL. We also found an increase in SUI of about 9% when we compared women with a very large uterus to those with small uterine

size. However, contrary to what we hypothesized, we did not find a stronger association between the presence of an anterior UL and SUI than UL in other locations.

Significance

The findings of the first paper suggest that future studies of the etiology of UL should distinguish focal UL subtypes (such as submucosal UL and intramural/subserosal UL) from the diffuse only subtype because of possible different etiologic mechanisms. In particular the different association seen between current smoking and the diffuse only subtype provide motivation for the study of this subtype as a separate entity, to better understand the biological cause of the diffuse heterogeneous echopattern seen on sonograms.

Very little is known about the pathophysiology of the diffuse only subtype. The diffuse heterogeneous echo pattern associated with this subtype may result from multiple small focal UL, or from larger UL that lack the usual distinct histological demarcation from the surrounding myometrium. Although many radiologists/sonographers may not include the presence of a diffuse heterogeneous echopattern as part of the definition of UL, we considered the diffuse heterogeneous echo pattern as a UL subtype because like focal UL, in the NIEHS UFS it is associated with enlargement of the uterus (Baird et al. 2003) and excess bleeding (Wegienka et al. 2003). Adenomyosis also can present as a diffuse heterogeneous echo pattern, but adenomyosis is usually accompanied by UL in uteri > 280g and occurs alone in only a minority of smaller uteri (LevGur 1996).

One important finding from the first paper is the absence of major differences between the risk factor profile of the two focal UL subtypes, despite documented histopathologic evidence that there are differences between the submucosal UL and the intramural or

subserosal UL beyond their anatomic position within the myometrium. Another very interesting finding is the strong inverse association of full-term pregnancies after age 24 with submucosal UL (stronger than the association with intramural/subserosal UL). One possible explanation may be the expulsion of submucosal UL with birth and postpartum remodeling of the uterus.

The findings from the second paper suggest that treatment for larger UL might enhance SUI treatment in some women. Similar to five previous epidemiological studies (Brown et al. 1999, Jackson et al. 2004, Handa et al. 2004, Hendrix et al. 2005, and Thom et al. 2006), the present study is investigating SUI in both African-American and Caucasian women, and provides further information on the association between ethnicity and SUI, in addition to information on the association of SUI with age, BMI, and parity.

Strengths and Limitations

NIEHS Uterine Fibroid Study participants, both African-American and Caucasian, were screened to identify UL among randomly selected premenopausal women irrespective of clinical symptoms. Consequently, women with both symptomatic and asymptomatic UL could be accurately classified according to UL presence and characteristics. This is important because UL may cause symptoms even when undiagnosed, and studying only symptomatic UL may be more likely to identify risk factors associated with growth than with incidence. Another important strength of the study is the detailed sonogram data that includes data on uterine size, uterine shape, the presence of diffuse heterogeneous echo pattern, number of focal UL, the size and location of the two largest UL, and the size of the three largest submucosal UL.

Limitations include the cross-sectional nature of the studies, which does not allow us to establish the temporality of the relationships under investigation. In particular we cannot evaluate risk factors for incident (versus prevalent) UL, and cannot confirm that UL preceded the onset of SUI symptoms. There are also limitations related to looking only at the size of the largest UL, and not being able to look at the number of UL. Considering the uterine size may have partly offset these limitations by providing a measure of the overall burden of UL. Also, the Caucasian women included in our study populations tended to be of low parity and high socioeconomic status, which may make the findings not generalizable to US Caucasian women of high parity and/or low socioeconomic status.

Direction for Future Research

The results of the first paper suggest treating the diffuse only subtype as a separate entity from the focal UL subtypes in future etiologic investigations. Although there is histopathologic evidence that the two focal UL subtypes are different from each other, more work also needs to be done to investigate potential differences between the two focal UL subtypes and the diffuse only subtype. An interesting related question would be to see if women can self-report the type of UL they have been diagnosed with.

Although we have investigated the association with risk factors consistently associated with focal UL, it is possible that other risk factors that have shown inconsistent results with respect to their association with focal UL may have different associations with the focal UL subtypes (submucosal UL and intramural/subserosal UL). Data on other potential risk factors were collected in the NIEHS Uterine Fibroid Study, such as oral contraceptives and reproductive tract infections, that do not show strong overall relationships

with UL, but could be investigated in relation to UL subtypes in the future. As more research is done to characterize the biological variation in UL, there may be alternative ways to examine this potentially heterogeneous outcome than by the three subtypes examined here. It should be noted that larger studies would be needed to be able to examine risk factors for UL subtypes than for UL presence (all subtypes combined).

The second paper provided preliminary evidence supporting a role of UL in the etiology of SUI, though contrary to expectations, location in the anterior uterus was not clearly associated with SUI. Although those findings suggest that treatment for larger UL might enhance SUI treatment in some women, they do not shade any light on what needs to be known in order to determine whether or when treatment of UL in order to treat SUI is appropriate to recommend. The later issue is very important from a public health point of view, and one possibility to deal with that will be for more studies to collect data specifically on self-reported SUI before and after UL treatment, and look at changes in the prevalence of SUI.

The NIEHS Uterine Fibroid Study includes data regarding "how much of a problem" SUI was, with the options given as: "not a problem", "a small problem", "a medium problem", and "a big problem", therefore future analyses may investigate UL characteristics in association with severity of self-reported SUI. Another possibility would be to examine associations between UL characteristics and urinary urgency, which was assessed in relation to the same reference period as SUI by the following question: "Have you felt the need to urinate urgently, even though you have had little or no warning?" Although this question does not directly assess urge urinary incontinence, which requires urine leakage in addition to urgency, it would add additional information regarding potentially relevant symptoms.

Therefore, the consideration of severity of self-reported SUI and of the presence of self-reported urgency would provide more insight into the relationship between UL characteristics and urinary symptoms that may substantially impact quality of life.

REFERENCES

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 Jan;188:100-107.

Brosens I, Deprest J, Dal CP, Van dH. Clinical significance of cytogenetic abnormalities in uterine myomas. Fertil Steril. 1998;69:232-235.

Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol. 1999;94:66-70.

Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003 Jun;111:1037-1054.

Handa VL, Harvey L, Fox HE, Kjerulff KH. Parity and route of delivery: does cesarean delivery reduce bladder symptoms later in life? Am J Obstet Gynecol. 2004 Aug;191:463-469.

Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, Aragaki A, Naughton MJ, Wallace RB, McNeeley SG. Effects of estrogen with and without progestin on urinary incontinence. JAMA. 2005 Feb 23;293:935-948.

Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, Simonsick EM, Brown JS. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol. 2004 Aug;104:301-307.

LevGur M. The enlarged uterus. Relation of uterine size to symptoms and histopathologic findings. J Reprod Med. 1996;41:166-170.

Marugo M, Centonze M, Bernasconi D, Fazzuoli L, Berta S, Giordano G. Estrogen and progesterone receptors in uterine leiomyomas. Acta Obstet Gynecol Scand. 1989;68:731-735.

Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstet Gynecol. 2002 Dec;100:1230-1238.

Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol. 2001 Jun;44:364-371.

Thom DH, van dK, Ragins AI, Wassel-Fyr C, Vittinghof E, Subak LL, Brown JS. Differences in prevalence of urinary incontinence by race/ethnicity. J Urol. 2006

Jan;175:259-264.

Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, Schectman JM, Hartmann KE. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101:431-437.