

Hypertension and pelvic inflammatory disease in women with leiomyomata: evidence from Germany and Finland

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Abstract

Objective: To explore the association between hypertension, pelvic inflammatory disease and uterine leiomyomata (UL).

Methods: A total of 2,799 women aged 40-69, randomly drawn from the popular register, were interviewed in Bremen, Germany, about their medical and gynecological history including UL, hypertension, history of diabetes and pelvic inflammatory disease (PID). A population sample of Finnish women (N=2,155) of similar age were interviewed for similar information as German women. The prevalences and odds ratios (OR) were adjusted for body mass index (BMI) and diabetes.

Results: The prevalence of UL in Germany was 27%, in Finland 30% and prevalence of hypertension 25% in Germany and 32% in Finland. The age-adjusted OR of UL was 1.3 (95% CI: 1.04-1.54) among hypertensive German women and 1.1 (95% CI 0.7-1.8) among hypertensive Finnish women. Hypertension among women with UL was more common among German women (age-adjusted OR 1.3 (95% CI 1.0-1.6) than among Finnish women (age-adjusted OR 0.99, 95% CI: 0.80-1.2). The history of PID was the strongest risk factor for UL among both German and Finnish women (German OR: 1.9, 95% CI: 1.6-2.3, Finnish OR 1.7, 95% CI: 1.4-2.1).

Conclusions: Both in Germany and in Finland hypertension and PID are associated with the risk of UL. Although causality cannot be evaluated, PID and hypertension may be associated with UL formation by initiating an injury to endometrial lining.

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INTRODUCTION

Uterine leiomyomas (UL) are the most common benign gynecological tumors among premenopausal women and leading causes of hysterectomy (1). The etiology of UL, which are result of the dysregulated proliferation of uterine smooth muscle, is still poorly understood (2). The factors related to increase risk of UL are age forties (3), endogenous hormonal factors (early menarche increase and menopause decrease) (4-7), prenatal estrogen exposure (8), family history (9, 10), African-American ethnicity(11, 12), genetic (13, 14), overweight (15-17) and tissue injury (18). While exercise (19, 20), higher parity(17, 21-23) and smoking (24-26) decrease the risk. There are conflicting results

regarding oral contraceptives (4, 27, 28).

Most recent hypotheses concerning UL etiology include the possibility of UL as markers of 'pro atherogenic state' and the role of local irritants and infection agents in UL pathogenesis (7, 29). Infectious agent might be the source of injury, especially for submucous leiomyomas, in which an ascending route of infection is most apparent. Pelvic inflammatory disease (PID) is a generic term for inflammation of the female uterus, fallopian tubes, and/or ovaries as it progresses to scar formation with adhesions to nearby tissues and organs. This may lead to tissue necrosis with/or without abscess formation (30). It is a common and serious complication of some sexually transmitted diseases (STDs), especially Chlamydia and gonorrhea (31).

On the other hand, several studies suggest that hysterectomized women are more often hypertensive when compare to non-hysterectomized women (32-35). Also

women who had undergone hysterectomy due to UL have higher prevalence of hypertension (35, 36). However, earlier studies have not taken into account possible risk factors, such as body mass index or diabetes.

Considering abovementioned studies, an interesting question is to compare UL, PID and hypertension prevalence and risk factors in different European Union countries. In case similarities are found, the associations may be explained by biological risk factors more than by country-specific discrepancies in gynaecological health services availability and functioning. Thus, the aim of this study was to analyze the associations between UL, hypertension and PID among German and Finnish women.

MATERIALS AND METHODS

GERMAN SAMPLE

A telephone survey was undertaken in 2000 in Bremen as part of a European Union project aiming to describe the prevalence of hysterectomy. A survey performed in the city of Bremen (total female population of 107,749 in 1999 aged 40-69 years) included a representative sample of 4,406 women aged 40-69, drawn randomly from the population register. Women were contacted by telephone or sent a questionnaire in case they did not have a listed telephone number. The interview comprised of 32 questions inquiring about medical history, menstrual history, parity, use of hormones, health status and socio-demographic factors. For women not willing to answer the "long" questionnaire, a "short" questionnaire comprising of eight questions was offered. Foreigners were included. An English translation of the "long" questionnaire was available as well as a Turkish and a Russian version of the "short" questionnaire.

By December 31, 2000, 2,872 completed "long" interviews had been collected plus an additional 193 German language "short" questionnaires plus 106 foreign language "short" questionnaires (total response rate 70.1%). N=78 interviews had to be deleted of women being either 39 or 70 years old on the day of the interview, as day and month of birth could not be made available from the population register and could only be obtained from persons interviewed (N=2,799). Including these interviewees, the overall response rate would have been 72.0

In the German survey ever diagnosis of myoma as well as hypertension was inquired similarly as in the Finnish survey. Also the year of the both diagnoses was asked and reported. Women could report myoma also as a reason for

hysterectomy.

In order to analyze the risk factors of women with myomas and without myomas, women with myomas were defined as cases and women without myomas as controls. Conditional logistic regression adjusted by age was used in order to compare women with and without myomas. In the question of history of hypertension cases and controls were adjusted not only by age but also by body mass index (BMI) and diabetes mellitus (DM). Such as diagnosis of hypertension, also BMI and DM were self-reported based on the question "Has a physician ever diagnosed hypertension /diabetes". Risk ratios on the basis of case-control analyses were calculated. The same was done to analyze the risk factors of women with and without hypertension.

In order to analyze the association between myoma and hypertension, hypertensive women were defined as cases and non-hypertensive women as controls. Each hypertensive woman (case) was then assigned one age-matched control. Odds ratios based on matched-pairs analysis were calculated in both time sequence possibilities: hypertension diagnosed before myoma and myoma diagnosed before hypertension.

FINNISH SAMPLE

A population sample of Finnish men and women 30-90 years of age (N= 8,028), drawn from the population register, underwent a home-based interview and clinical health examination by physicians during 2000-2001. The history of hypertension and diabetes was based on self-reports during the interview. Response rate was 87.6% for interview and 79.7% for health examination.

There were 2,125 women aged 40-69 in the sample (37). The survey in the year 2000 included separate sections for reproductive health, surgery and history of infections. History of hypertension, UL and PID were based on self-reports. Analysis of Finnish sample was similar than the analysis with German sample.

RESULTS

Among German women the self-reported proportion of UL was 27.3% and hypertension 24.8%, and among Finnish women 29.7% and 32.3%. 24.8% of the German and 15.8% of the Finnish women had undergone hysterectomy. The proportion of German women with UL was highest in the age group of 50-54 years (38.2%) and among Finnish women of 65-69 years (36.8%). The discrepancy may be explained by the higher proportion of hysterectomized

German women among older women and possible recall bias. The proportion of women with UL was lowest in the age group of 40-44 years in both groups of women (15.5% and 16.9%). The age-adjusted proportion of women with hypertension was higher among Finnish as compared to German women (Table 1).

Figure 1

Table 1: Distribution of hysterectomy, uterine leiomyoma and hypertension by age in German (N=2762) and Finnish (N=2125) samples

Age group	Uterine leiomyomas (%)		Hypertension (%)		Hysterectomy (%)		Total	
	Germany	Finland	Germany	Finland	Germany	Finland	Germany	Finland
	N=753	N=626	N=686	N=682	N=694	N=334	N	N
40-44	15.5	16.9	8.7	15.7	5.9	6.1	505	396
45-49	23.9	29.5	14.1	24.0	12.2	12.8	461	450
50-54	38.3	30.1	23.6	30.3	24.7	16.5	434	422
55-59	30.2	33.7	26.5	42.0	32.1	22.9	483	314
60-64	30.3	35.4	35.5	43.7	37.1	21.3	501	299
65-69	26.7	36.8	44.3	49.6	39.9	19.0	378	244
Total: 40 - 69	27.3	29.7	24.8	32.3	24.8	15.8	2762	2125

The average age of the German women with myomas was 55.2 years (SD 7.6) and the women without myomas 53.6 years (SD 8.8). Among Finnish women with myomas the average age was 54.7 (SD 8.0) and without myomas 52.4 (SD 5.3). Women with UL were more often nulliparous and had lower parity than women without UL (Table 2). Finnish women were more often overweight than German women.

Figure 2

Table 2. Age-adjusted risk factors of women with and without uterine leiomyoma (UL) among German (GER) and Finnish (FIN) samples

	Women with UL		Women without UL		OR		95% CI	
	Ger	Fin	Ger	Fin	Ger	Fin	Ger	Fin
	N=753	N=626	N=2009	N=1499				
Age at menarche (years) ^a	%	%	%	%				
8-10	1.4	1.8	1.7	1.3	0.85	1.42	0.40-1.80	0.67-3.02
11	8.4	8.4	7.3	8.3	1.15	1.00	0.80-1.67	0.68-1.46
12	18.5	18.2	17.6	17.1	1.00	1.00		
13	22.6	23.9	23.0	26.8	0.94	0.83	0.72-1.24	0.65-1.06
14-17	49.2	47.7	50.5	46.5	0.91	0.87	0.72-1.16	0.68-1.12
Ever pregnant ^b								
Yes	80.3	87.9	82.7	89.7	0.80	0.81	0.64-1.00	0.61-1.07
No	19.7	12.1	17.3	10.3	1.00	1.00		
Parity ^c								
0	19.7	15.2	17.3	13.0	1.00	1.00		
1	25.4	22.5	23.3	18.3	0.92	1.00	0.71-1.20	0.73-1.38
2	34.0	32.9	35.0	36.5	0.78	0.75	0.61-0.99	0.57-0.98
3	13.8	19.7	14.2	20.0	0.77	0.80	0.57-1.05	0.55-1.16
4 or more	7.2	9.8	10.2	12.2	0.57	0.57	0.39-0.82	0.38-0.84
Body Mass Index (kg/m ²) ^d								
< 20 (underweight)	6.5	2.4	7.3	4.4	0.88	0.58	0.62-1.25	0.31-1.05
20 - 24 (normal weight)	49.3	34.5	47.2	34.3	1.00	1.00		
25 - 29 (mild overweight)	31.1	35.5	32.8	34.7	0.82	0.93	0.68-1.00	0.75-1.16
30 + (overweight)	13.1	27.5	12.7	26.6	0.89	0.92	0.68-1.16	0.71-1.19
History of hypertension ^e								
Yes	29.4	34.3	22.8	31.4	1.27	0.99	1.04-1.55	0.80-1.22
No	70.6	65.7	77.2	68.6	1.00	1.00		
History of diabetes mellitus ^f								
Yes	5.1	5.4	4.0	4.2	1.2	1.1	0.70-1.78	0.74-1.75
No	94.9	94.6	96.0	95.8	1	1		
History of pelvic inflammatory disease ^g								
Yes	28.6	38.5	16.9	27.8	1.9	1.7	1.56-2.33	1.35-2.06
No	71.4	61.6	83.1	72.2	1	1		
Use of oral contraceptives >12 months ^h								
Yes	64.4	53.2	63	55.2	1.1	1.1	0.91-1.32	0.91-1.33
No	35.6	46.8	37	44.8	1	1		
Use of HRT > 12 months ⁱ								
Yes	48.6	46.6	29.8	25.9	2	2.3	1.63-2.41	1.84-2.78
No	51.4	51.4	70.2	74.1	1	1		

^aMissing=31 (Ger), 18 (Fin)

^bMissing=3 (Ger), 5 (Fin)

^cMissing=3 (Ger), 5 (Fin)

^dMissing=15 (Ger), 22 (Fin)

^eMissing=33 (Ger), 3 (Fin)

^fMissing=23 (Ger), 5 (Fin)

^gMissing=19 (Ger), 261 (Fin)

^hMissing=5 (Ger), 23 (Fin)

ⁱMissing=7 (Ger), 3 (Fin)

However, German women with UL were more often

hypertensive than women without UL (OR 1.27, 95% CI 1.04-1.55). The association with UL and the history of hypertension sustained after adjusting for age and BMI (OR 1.34, 95% CI 1.09-1.65), age and diabetes (OR 1.26, 95% CI 1.03-1.55) and for age, BMI and diabetes (OR 1.32, 95% CI 1.07-1.63). Among Finnish women the association of UL and hypertension was not so clear (OR 0.99, 95% CI 0.80-1.22). Women with UL had more often diabetes in both German and Finnish groups (age-adjusted OR 1.19 and 1.14, 95% CI 0.70-1.78 and 0.74-1.75).

The strongest risk factor for UL was the history of pelvic inflammatory disease-, the risk ratio was 1.91 (95% CI 1.56-2.33) among German and 1.67 (95% CI 1.35-2.06) among Finnish women. The use of hormone replacement therapy was more frequent among women with UL (OR 1.98, 95% CI 1.63-2.41 and OR 2.26, 95% CI 1.84-2.78).

As expected, German women with hypertension were older (average age 58.2 years, SD 7.6) than women without hypertension (average age 52.7 years, SD 8.4). Also in the Finnish sample the hypertensive women were older (average age 56.0 years, SD 8.0) than other women (average age 51.7 years, SD 5.0). Women with hypertension were more often overweight than women without hypertension in both groups (Table 3). The adjusted history of diabetes mellitus is four to five times more common among hypertensive than non-hypertensive women. Hypertensive German women have more often UL (OR 1.26, 95% CI 1.04-1.54) and they also had undergone more often hysterectomy (OR 1.47, 95% CI 1.20-1.79) but the association is not so clear among Finnish women (OR 1.14, 95% CI 0.74-1.75 and OR 1.14, 95% CI 0.88-1.47). The history of ovarian removals did not differ between the groups.

Figure 3

Table 3: Age-adjusted risk factors of women with and without hypertension

	Women with hypertension		Women without hypertension		OR		95% CI	
	Ger N=686	Fin N=682	Ger N=2078	Fin N=1443	Ger	Fin	Ger	Fin
Body Mass Index (kg/m ²) ^a	%	%	%	%				
< 20	3.1	1.6	8.3	4.8	0.73	0.61	0.43-1.19	0.30-1.25
20-24	30.3	22.1	33.3	40.2	1.00	1.00		
25-30	42.0	36.2	29.2	34.3	2.13	1.92	1.72-2.63	1.53-2.40
>= 30	24.6	40.1	9.1	20.7	4.15	3.53	3.18-5.41	2.78-4.49
History of diabetes mellitus ^b								
Yes	11.2	9.1	2.1	2.4	4.95	4.10	3.29-7.46	3.29-7.46
No	88.8	90.9	97.9	97.6	1.00	1.00		
History of myoma ^c								
Yes	32.7	31.5	25.7	28.8	1.26	1.14	1.04-1.54	0.74-1.75
No	67.3	68.5	74.3	71.2	1.00	1.00		
History of hysterectomy								
Yes	36.3	18.6	21.1	14.5	1.47	1.14	1.20-1.79	0.88-1.47
No	63.7	81.4	78.9	85.5	1.00	1.00		
Removal of one ovary (with or without hysterectomy) ^d								
Yes	6.8	2.9	6.6	2.3	0.85	0.99	0.60-1.22	0.55-1.81
No	93.2	97.1	93.4	97.7	1.00	1.00		
Removal of both ovaries (with or without hysterectomy)								
Yes	10.2	4.7	5.8	3.8	1.15	0.95	0.83-1.58	0.60-1.51
No	89.8	95.3	94.2	96.2	1.00	1.00		

^aMissing=14 (Ger), 19 (Fin)

^bMissing=26 (Ger), 2 (Fin)

^cMissing=35 (Ger), 3 (Fin)

^dMissing=22 (Ger)

DISCUSSION

In our study both history of PID and hypertension were associated with risk of UL independent of other factors like age, BMI and diabetes. A possible explanation for the relation between UL and PID could be a local tissue damage which would lead myometrial tissue to an abnormal growth. Our finding is in line with earlier studies reporting the history of PID and chlamydial infection as risk factors for UL (29). Infectious processes or chronic inflammation are associated with the development of several neoplasms (38, 39). The potential role of infection in UL development can also be postulated in the context of similarities between this tumor and the atheromatous plaque, because of the suggestion that chlamydial and viral infections play a role in atherosclerosis (40, 41). There is some other suggestion of similarities between a tumor of smooth muscle cells like UL and the atheromatous plaque. A key event in plaque formation is also smooth muscle cell proliferation, which is induced by atherogenic risk factors such as hypertension and diabetes mellitus (42).. UL has a monoclonal origin (43), same as atheromatous plaque (44) cells from both conditions behave identically in culture (45). Uterine smooth muscle cells in toxemia of pregnancy can accumulate intracytoplasmic lipid, simulating the basic structure of the atheromatous lesion (46) and the fact which atherosclerosis is also an inflammatory disease (47, 48). An infectious agent might be the source of injury, especially for submucous leiomyomas, in which an ascending route of infection is most apparent.

Our data could not show a strong relationship between

hypertension and UL. Only in Germany a marginally significant correlation was found. Possibly due to the different age-distribution of Finnish women with myomas the association was weaker than in German women. In Finnish data the association between myomas and hypertension sustained after taking into account other risk factors, such as BMI and the history of diabetes. The hypertensive women have been hysterectomized more often than other women independent of their age and myomas are a usual indication for an operation. Similar findings have been shown in earlier studies. In the study of Koepsell et al (32) hysterectomized women aged 35-74 years had a 45.5% age-adjusted prevalence of hypertension. In the Danish study the history of hypertension was also a closely related risk factor for premenopausal hysterectomy performed for benign diseases (33). Luoto et al (34) found also that hysterectomy with preservation of at least one ovary was associated with an increased risk of high diastolic blood pressure and diagnosis of hypertension. The coexistence of UL and hypertension was also found in other studies (29, 35). Women with UL had a 1.7-fold adjusted risk for a history of hypertension and a 2.1-fold adjusted risk for the use of anti hypertensive medication (29). UL were more frequent among hypertensive women than normotensive women in the Finnish study (35). However, earlier studies have not taken into account possible risk factors, such as body mass index or diabetes. There is increasing evidence that Angiotensin II (Ang II), a major regulator of blood pressure and cardiovascular homeostasis, is involved in the regulation of cell proliferation, angiogenesis, inflammation and tissue remodeling (49). A prospective study showed that elevated blood pressure has an independent, positive association with risk for clinically detected uterine leiomyoma among premenopausal woman (50). Elevated blood pressure may cause smooth muscle cell injury and cytokine release and increase the risk of leiomyomata, in a process analogous to atherosclerotic changes in arterial smooth muscle cells. In addition to causing vasoconstriction, Ang II affects the transcription of multiple genes concerned with cell proliferation, angiogenesis, inflammation and atherogenesis or thrombus formation. Ang II-induced leiomyoma cell proliferation may play a crucial role in the association of hypertension and uterine leiomyoma. A experimental findings in vitro highlight the potential role of Ang II in the proliferation of leiomyoma cells (51).

Both German and Finnish samples were based on self-reports of myomas and hypertensive disease. To our

knowledge, except a study by Schwarz there is no previous population-based study providing insights into prevalence of specified gynecological procedures including hysterectomy in Germany (52). However, their data did not provide information on indication of the hysterectomy (benign or non-benign reasons). In the Finnish study physicians performed health examination without gynaecological status. These methodological differences may partly explain the observation between hypertensive women with myomas. Since self-reported information was not checked from any appropriate medical records, information on diagnostic methods, a uterine sonogram or possible histological findings after the hysterectomy are lacking. On the other hand, both Germany and Finland samples were of similar size and had nearly equal prevalence of UL. Higher prevalence of hypertensive women by age is in line with previous findings. Also in both samples the association between PID and UL was found, increasing the possibility of biological pathogenesis in UL formation rather than other explanations related to availability of gynaecological services or other health services related issues. Health services patterns or methodological discrepancies (survey vs interview) and the fact that hysterectomized women may have been under more intense medical observation than women who have not had this procedure may increase the possibility of diagnosis of hypertension and UL and possibly more vascular disease after hysterectomy. Our cross-sectional study has many weaknesses in order to explain this possible pathogenic association between myomas and hypertension. A longitudinal study among women who have a diagnosed myoma might provide further information about this association. Women should be followed for years and a 24-hour blood pressure measurement should be done at the beginning and during of the follow-up. If women are hysterectomized during the follow-up the uterus should be analyzed for growth factors.

Although pathogenesis of uterine myomas presently are not well understood, many advances have been made in the understanding of the hormonal factors, genetic factors, growth factors, and molecular biology of these benign tumors (3, 53). Finnish researchers have reported hereditary analyses regarding UL (54). The earlier reported risk factors for myomas include obesity, early menarche and the history of infertility (7). Risk for myomas have decreased with increasing duration of use of oral contraceptives (7, 15) but the opposite has also been found (21). Leiomyomas are hormone dependent so they can continue to grow after

menopause if HRT is used. Estrogen and progesterone are known to regulate the growth of uterine myomas and it is believed in part to be mediated by growth factors which include insulin-like growth factor I (IGF-1) (55-58), epidermal growth factor (EGF) (59) and endothelia (60). The local growth factors may be involved in myoma cell proliferation and lead to development of myomas. In addition to growth factors Matsumoto et al (61) reported that leiomyomas express also angiotensin II receptors. Angiotensin II is an important substance in the regulation of the blood pressure and kidney function. Several of these growth factors have an influence on vascular smooth muscle cells and blood pressure. The above mentioned factors, possibly together with obesity, insulin resistance or hyperinsulinemia, might be involved in a common pathogenic mechanism which would explain the association between myomas and hypertension.

PID is the most common reason for hospitalization for gynaecologic disorders among reproductive women in the US (62). As sexual transmitted diseases are increasing in the population level, the possibility of PID also increases. This trend may cause more irritation to uterine lining, parallel with the formation of hypertension and UL. The evidence from two European countries in our study supports the role of local irritation and inflammations in pathogenesis of UL. A longitudinal study among women who have a diagnosed PID might provide further information regarding pathogenesis of UL.

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