

PREVALENCE OF REPRODUCTIVE ABNORMALITIES AMONG WOMEN WITH FAMILIAL PARTIAL LIPODYSTROPHY

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ABSTRACT

Objective: To compare the risk of having polycystic ovary syndrome (PCOS) or ovarian cysts among women with genetically confirmed familial partial lipodystrophy (FPLD) with that in the general population of healthy women.

Methods: Twenty-five women with FPLD who were 18 to 80 years old were interviewed regarding a history of PCOS or ovarian cysts (composite primary outcome) as well as for secondary outcomes of interest including menstrual irregularities, hirsutism, gynecologic surgical procedures, and fertility or obstetric complications. From the 2005 National Ambulatory Medical Care Survey, 3,326 women, aged 18 to 80 years (control subjects), were assessed for the presence of the primary outcome based on appropriate *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Results: Four of the 25 patients with FPLD (16%) had a history of PCOS or ovarian cysts, in comparison with 14 of the 3,326 control subjects (0.42%), resulting in an age- and body mass index-adjusted odds ratio of 40.6 (95% confidence interval, 12.1 to 136.7; $P < .0001$) among the patients with FPLD. Furthermore, 5 women with FPLD (20%) required at least 1 oophorectomy during their lifetime, and 6 (24%) had had hysterectomies at a young age (≤ 55 years).

Conclusion: Women with genetically confirmed FPLD have an increased risk for PCOS and ovarian cysts, as well as early hysterectomies, in comparison with the general population. Therefore, timely involvement of gynecologists in the care of these patients is warranted. (*Endocr Pract.* 2008;14:000-000)

Abbreviations:

BMI = body mass index; **CGL** = congenital generalized lipodystrophy; **FPLD** = familial partial lipodystrophy; **HDL-C** = high-density lipoprotein cholesterol; **IL-6** = interleukin-6; **NAMCS** = National Ambulatory Medical Care Survey; **OR** = odds ratio; **PCOS** = polycystic ovary syndrome; **T2DM** = type 2 diabetes mellitus; **TNF- α** = tumor necrosis factor- α

INTRODUCTION

Polycystic ovary syndrome (PCOS) is currently the most prevalent endocrine disorder among reproductive-age women, affecting approximately 4% to 7% of this subset (1,2). Although several definitions exist, PCOS has been recently characterized by the presence of clinical and biochemical hyperandrogenism in conjunction with ovulatory dysfunction (3-6). Importantly, multiple ovarian cysts, documented with use of ultrasonography, can be seen in the context of PCOS and have also been included in the diagnostic criteria for PCOS (4-6).

Women with PCOS are at increased risk for fertility problems as well as the long-term complications of endometrial hyperplasia or cancer (7). Another major long-term complication of PCOS is type 2 diabetes mellitus (T2DM), mediated by insulin resistance (8). Women affected by PCOS have profound insulin resistance in comparison with age- and body mass index (BMI)-matched healthy control subjects (9). Although the exact pathogenesis for PCOS is unknown, insulin resistance has been postulated as an important mechanism for the clinical manifestations because insulin has been shown to induce ovarian cyst formation as well as ovarian steroidogenesis (10). Thus, insulin resistance itself may be a key mediator for the formation of ovarian cysts.

Insulin resistance is inherent to several disorders other than PCOS. In fact, one approach to understanding a complex phenotype such as PCOS is to study an extreme monogenic form of insulin resistance such as genetic lipodystrophies, which may also be characterized by polycystic ovaries. Of the genetic lipodystrophies, familial

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partial lipodystrophy (FPLD) is the most common, affecting approximately 1 in 200,000 (11). An autosomal dominant genetic lipodystrophy, FPLD is characterized by the loss of subcutaneous fat from the extremities and gluteal regions after the onset of puberty. It is also typified by severe insulin resistance and, frequently, the development of T2DM after the second decade of life (12,13). Although polycystic ovaries have been reported in several patients with FPLD, no study has documented the risk of having PCOS or ovarian cysts among female patients with molecularly characterized FPLD in comparison with that in the general population (13,14). Demonstrating a link between FPLD and polycystic ovaries has important implications not simply for surveillance of fertility or obstetric issues but also for prevention of long-term complications of T2DM or cardiovascular disease, which are already at increased prevalence among patients with FPLD. The association of FPLD with mutant forms of *LMNA*, which encodes the nuclear envelope protein lamin A/C, or *PPARG*, which encodes a nuclear hormone receptor, as causative for FPLD (15-19) may have implications for unraveling the genetic basis for the complex phenotype of PCOS or for the formation of ovarian cysts. Thus, in this report we describe the prevalence of PCOS or ovarian cysts among female patients with FPLD in comparison with that among a representative sample of healthy control subjects.

SUBJECTS AND METHODS

Study Subjects With FPLD

Female subjects 18 to 80 years old having clinical features consistent with FPLD from the clinic of a single investigator (R.A.H.) were interviewed regarding reproductive history. The primary objective of this study was to evaluate the number of women with FPLD who had a diagnosis of either PCOS or unilateral or bilateral ovarian cysts. Our secondary outcomes of interest were a history of menstrual irregularities, infertility, obstetric complications, hirsutism, and gynecologic surgical procedures. All subjects had genetically confirmed FPLD based on the presence of causative mutations in either the *LMNA* or *PPARG* genes. A total of 25 women who met these criteria were included in this study. Height, weight, blood pressure, BMI, plasma glucose, and a lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol) were determined in these study participants. The study of these subjects was approved by the University of Western Ontario Institutional Review Board.

Biochemical and Genetic Determinations for Study Subjects With FPLD

Assays of fasting plasma concentrations of total cholesterol, triglycerides, HDL-C, and glucose as well as calculation of low-density lipoprotein cholesterol levels were performed with use of established methods (20). For

extraction of DNA, previously described procedures were used (20). *LMNA* mutations were determined from genomic DNA with use of oligonucleotide primers 5'-GCAAGATACACCCAAGAGCC-3' and 5'-ACACCTGGGTTCCCTGTTC-3', whereas *PPARG* mutations were determined with use of the primers 5'-TTCAGTGTGAGTTAGAAATC-3' and 3'-CAATGCAGACTAACTAAGG-5' and application of previously described methods (15,16).

Control Subjects

Control subjects for the patients with FPLD were selected from the National Ambulatory Medical Care Survey (NAMCS) of 2005, a United States-based national survey outlining the use of ambulatory medical services determined on the basis of a sample of visits to non-federally employed office-based physicians (excluding anesthesiologists, pathologists, and radiologists) engaged in direct patient care. Through this survey, data are obtained on patients' symptoms, physicians' diagnoses, demographic characteristics of patients, and services provided, including information on diagnostic procedures and patient management. The survey instrument and summary statistics are available at the Centers for Disease Control Web site (21). Although weighted estimation procedures are available to produce results that reflect the entire population of the United States, we used unweighted rates as the appropriate comparator for the purposes of accurate determination of patients seen in clinics or offices for management of ovarian cysts or PCOS.

From the NAMCS, female subjects 18 to 80 years old were selected for further analysis. Of these 3,326 women, individuals were identified who had *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for PCOS (256.4) or ovarian cysts (620.0 or 620.2) in at least one of their diagnoses in the survey. Data regarding weight, height, BMI, and blood pressure were included for subjects from the NAMCS.

Statistical Analysis

Quantitative clinical traits of age, weight, BMI, and blood pressure were compared between patients with FPLD and control subjects with use of the Student *t* test from the general linear models procedure in SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina). Data are expressed as mean \pm standard deviation. The ratio of individuals with PCOS or ovarian cysts among patients with FPLD was compared with that among control subjects by using logistic regression with age and BMI as covariates. A value of $P < .05$ was considered the nominal level of significance for all comparisons.

RESULTS

Baseline Characteristics

Twenty-five FPLD-affected patients and 3,326 control subjects fulfilled the criteria for inclusion in the study.

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Age was not significantly different between the FPLD-affected patients and the control subjects. In comparison with control subjects, FPLD-affected patients demonstrated significantly lower values for BMI (25.0 ± 3.3 versus 29.0 ± 8.2 kg/m²; $P < .0001$; FPLD versus control) and weight (67.5 ± 10.3 versus 76.3 ± 20.6 kg; $P = .0004$; FPLD versus control). In contrast, systolic and diastolic blood pressure values were significantly higher among the patients with FPLD in comparison with the control subjects (Table 1).

Genotyping of the 25 patients with FPLD demonstrated *LMNA* mutations in 24, with 22 possessing the most common R482Q mutation. The sole *PPARG* mutation represented in the FPLD population was *PPARG* F388L (Table 2).

Prevalence of PCOS or Ovarian Cysts

Among the 25 patients with FPLD, 3 (12%) had ovarian cysts and 1 (4%) was diagnosed with PCOS (Table 2). Thus, a total of 4 of the 25 patients with FPLD (16%) had a history of PCOS or ovarian cysts in comparison with 14 of the 3,326 control subjects (0.42%), resulting in an odds ratio (OR) for PCOS or ovarian cysts among those with FPLD of 40.6 (95% confidence interval, 12.1 to 136.7; $P < .0001$). Among those who had PCOS or ovarian cysts, the age was significantly higher among the FPLD-affected patients in comparison with the control subjects (51.8 ± 7.9 versus 39.1 ± 12.3 years, respectively; $P = .04$). Comparison of weight, BMI, and blood pressure values between the FPLD and control groups revealed no statistically significant differences (Table 3). Patients with FPLD who had PCOS or ovarian cysts had significantly lower HDL-C levels in comparison with patients with FPLD who did not have PCOS or ovarian cysts (0.90 ± 0.13 versus 1.16 ± 0.35 mmol/L, respectively; $P = .03$); no other significant differences with respect to age, BMI, weight, or blood pressure variables were noted (data not shown).

Prevalence of Other Reproductive Abnormalities

An additional 8 women (32%) had menstrual irregularities, and 5 (20%) required at least 1 oophorectomy during their lifetime. Seven women (28%) had hysterectomies, with 6 (24%) having had a hysterectomy at a young age (≤ 55 years). Although only 6 patients answered affirmatively for having hirsutism, a clinical phenotype of PCOS based on the presence of irregular menses and hirsutism without obvious cause was found in 4 women, in addition to the 1 patient who already had a confirmed diagnosis of PCOS. Obstetric or fertility problems among patients with FPLD included 1 patient experiencing infertility and another having had 2 miscarriages.

DISCUSSION

In comparison with a representative sample of the general population, FPLD is associated with an increased risk for PCOS or ovarian cysts. The association of ovarian cysts or PCOS with congenital lipodystrophies has been previously reported, primarily in the context of congenital generalized lipodystrophy (CGL) because CGL-affected persons typically demonstrate several shared features with PCOS, including insulin resistance, acanthosis nigricans, and hyperandrogenism (13,22). In contrast with CGL, however, FPLD is much more prevalent and is associated with a less severe but still considerable degree of insulin resistance. Thus far, the coexistence of PCOS or ovarian cysts among FPLD-affected women has been thought to be uncommon, partly attributable to sporadic reporting (13,14).

Recent data suggest that PCOS is indeed common among FPLD-affected women. Vantyghem et al (23) demonstrated that 7 of 13 FPLD-affected women (*LMNA* mutations only) (54%) had a clinical phenotype of PCOS based on the presence of scanty menorrhagia and hirsutism with no other identified cause. Furthermore, fertility or

Table 1
Baseline Characteristics of
Familial Partial Lipodystrophy-Affected Women and Control Subjects^a

Entire population (N)	Age (y)	Weight (kg)	BMI (kg/m ²)	Blood pressure (mm Hg)	
				Systolic	Diastolic
NAMCS (control subjects) (3,326)	49.8 ± 16.8	76.3 ± 20.6	29.0 ± 8.2	125 ± 18	75 ± 11
Patients with FPLD (25)	46.5 ± 16.2	67.5 ± 10.3^b	25.0 ± 3.3^b	135 ± 21^b	83 ± 13^b
<i>P</i> value	.32	.0004	<.0001	.03	.009

^a BMI = body mass index; FPLD = familial partial lipodystrophy; NAMCS = National Ambulatory Medical Care Survey.

^b Data available for only 24 patients.

Table 2
Reproductive and Biochemical Status of
Familial Partial Lipodystrophy-Affected Patients^a

Case	Age (y)	BMI (kg/m ²)	Genotype	Ovarian cysts or PCOS	Irregular menses	Hirsutism	Other reproductive variables	SBP ^b	DBP ^b	TC ^c	TG ^c	HDL ^c	LDL ^c
1	18	20.2	LMNA R482Q	N	N	N	N	116	68	4.9	1.06	1.1	3.3
2	16	25.3	LMNA R482Q	N	N	Y	N	114	84	4.62	2.7	1.03	2.4
3	44	26.2	LMNA R482Q	N	N	N	N	112	72	4.52	0.8	1.73	2.4
4	57	23.5	LMNA R482Q	N	N	N	N	130	82	4.93	2	1.1	2.9
5	63	25.3	LMNA R482Q	N	N	N	N	145	94	5.55	3.2	1.02	3.1
6	63	20.5	LMNA R482Q	N	N	N	Hysterectomy (ovaries intact)	140	70	3.19	2.1	1.14	1.1
7	62	21.4	LMNA R482Q	N	N	N	N	156	92	3.02	1.72	0.82	1.41
8	66	22.4	LMNA R482Q	N	N	N	N	160	100	6.67	1.48	1.68	4.7
9	68	24.5	LMNA R482W	N	N	N	N	140	90	NA	NA	NA	NA
10	26	25.3	LMNA R482Q	N	N	Y	N	134	78	3.32	0.44	1.21	1.86
11	52	24.3	LMNA R482Q	N	N	N	Hysterectomy at 40 y	102	61	5.22	1.38	0.94	4.53
12	20	26.5	LMNA R482Q	N	Y	N	N	150	100	4.26	3.65	0.69	1.91
13	27	34.5	LMNA R482Q	N	Y	Y	N	NA	NA	6.1	17.63	NA	NA
14	31	27.7	LMNA R482Q	N	Y	Y	Infertility	136	75	NA	NA	NA	NA
15	32	28.2	LMNA R482Q	N	Y	N	N	124	80	5.04	2.14	1.53	2.54
16	38	22.6	LMNA R482Q	N	Y	N	N	140	90	NA	NA	NA	NA
17	51	24.1	LMNA R482Q	N	N	N	TAHBSO	155	95	4.93	3.62	0.94	2.3
18	48	NA	LMNA R482Q, V440M	N	Y	Y	UO, hysterectomy at 40 y	200	100	12.35	26.34	0.64	NA
19	53	31.3	LMNA R482W	N	Y	Y	N	134	80	5.05	1.77	1.05	3.2
20	57	21.4	LMNA R482Q	N	N	N	UO, hysterectomy at 55 y	124	74	7.44	1.1	1.83	5.1
21	64	22.7	LMNA R482Q	N	Y	N	N	140	90	5.88	2.73	1.38	3.8
22	54	25.0	LMNA R482Q	Y (PCOS)	Y	N	Hysterectomy at 30 y	140	105	4.22	3.79	1.09	1.41
23	46	25.9	LMNA R482Q	Y (MOC)	N	N	UO	116	60	4.96	1.9	0.86	3.2
24	45	26.4	PPARG F388L	Y (BOC)	N	N	2 miscarriages	108	78	3.49	2.73	0.88	2
25	62	25.3	LMNA R482Q	Y (UOC)	N	N	BSO at 35 y, hysterectomy at 27 y	130	70	2.41	1.06	0.78	1.15

^a BMI = body mass index; BOC = bilateral ovarian cysts; BSO = bilateral salpingo-oophorectomy; DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; LMNA = lamin A; MOC = multiple ovarian cysts; N = no; NA = not available; PCOS = polycystic ovary syndrome; PPARG = peroxisome proliferator-activated receptor gamma; SBP = systolic blood pressure; TAHBSO = total abdominal hysterectomy with bilateral salpingo-oophorectomy; TC = total cholesterol; TG = triglycerides; UO = unilateral oophorectomy; UOC = unilateral ovarian cyst; Y = yes.

^b Measured in mm Hg.

^c Measured in mmol/L.

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Table 3
Prevalence of Polycystic Ovary Syndrome or Ovarian Cysts
Among Familial Partial Lipodystrophy-Affected Women and Control Subjects^a

Group	With PCOS or ovarian cysts, n (%)	Age (y)	Weight (kg)	BMI (kg/m ²)	Blood pressure (mm Hg)	
					Systolic	Diastolic
NAMCS (control subjects)	14 (0.42)	39.1 ± 12.3	72.2 ± 16.2	26.3 ± 10.1	112 ± 35	69 ± 23
Patients with FPLD	4 (16)	51.8 ± 7.9	67.8 ± 6.0	25.6 ± 0.7	124 ± 14	78 ± 19
Odds ratio = 40.6 ^b						
<i>P</i> value	<.0001	.04	.42	.81	.35	.43

^a BMI = body mass index; FPLD = familial partial lipodystrophy; NAMCS = National Ambulatory Medical Care Survey; PCOS = polycystic ovary syndrome.

^b Age- and body mass index-adjusted odds ratio; 95% confidence interval, 12.1-136.7.

obstetric complications were common in these women, with 50% having at least 1 miscarriage and 36% developing gestational diabetes. From our own data, 16% of the FPLD-affected women demonstrated PCOS or ovarian cysts, yielding an age- and BMI-adjusted OR of 40.6, in comparison with the non-FPLD-affected women. If our definition of PCOS were expanded to match that of Vantyghem et al (23) (that is, to include those women with a clinical phenotype of irregular menses and hirsutism without another obvious cause), the percentage of our FPLD-affected women with PCOS or ovarian cysts would increase to 32% (OR, 90.6; 95% confidence interval, 31.4 to 261.6). In addition, 7 of 25 women (or about 1 in 4) from our report had hysterectomies, and 6 of these 7 had their hysterectomies at age 55 years or younger. In contrast, hospitalization data from the United States National Hospital Discharge Survey revealed that 1 in 196 female patients 15 years old or older had hysterectomies in 2004 (24). Thus, FPLD-affected women either had a prevalence of ovarian cysts or PCOS or had a need for hysterectomy that is several orders of magnitude higher than that among women without FPLD. Therefore, FPLD is indeed commonly associated with reproductive disorders.

Because the patients with FPLD in our report demonstrated lower BMI and weight in comparison with non-FPLD control subjects, the increased risk of PCOS or ovarian cysts is not likely attributable to differences in fat mass. Instead, the increased risk for PCOS or ovarian cysts is more likely due to differences in adipose distribution and the presence of insulin resistance. When compared with healthy BMI-matched control subjects, both PCOS-affected and FPLD-affected patients demonstrate increased visceral adipose tissue, which is strongly related to insulin resistance (25,26). Increased visceral adipose tissue is typically associated with altered secretion of sev-

eral adipocytokines, including adiponectin, leptin, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6). Of these, adiponectin and IL-6 are inversely associated with insulin resistance through effects on insulin signaling, endogenous glucose production, and fatty acid oxidation, whereas TNF- α is directly correlated with insulin resistance (27-30). Patients with FPLD have lower adiponectin, leptin, and IL-6 and higher TNF- α levels in comparison with control subjects (31). Collectively, these data suggest that altered adipose distribution and adipocytokine levels among FPLD-affected patients promote the development of insulin resistance, which in turn may provide an environment conducive to development of ovarian cysts and PCOS.

Our report has a few limitations. Data from the NAMCS represented ambulatory clinic visits within the United States and are dependent on accurate coding of visits by clinicians. There may be women who were seen in consultation for PCOS or ovarian cysts but not coded for these disorders in their visits; this situation would account for the discrepancy of the prevalence of PCOS among control subjects in this report of 0.42% in comparison with the value of 4% to 7% often quoted from other reports (1,2). More importantly, the NAMCS does not include values for lipoprotein variables or insulin levels. Thus, comparisons between patients with FPLD and control subjects with respect to these variables were not possible. Because data for patients with FPLD were obtained by questionnaire screening alone, it is highly likely that ultrasonography of our patients with FPLD would have detected a higher percentage of ovarian cysts among those women who demonstrated menstrual irregularities or hirsutism (or both). Similarly, access to pathologic examination of endometrial tissue and ovarian tissue from women who had undergone hysterectomies or oophorectomies would

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have been useful in determining whether there was evidence of endometrial hyperplasia or ovarian cysts, respectively. Despite these limitations, our report still demonstrates a significantly increased prevalence of ovarian cysts—either as isolated ovarian cysts or in the context of PCOS—among FPLD-affected women, confirming the results of a recent report (23). We have also shown that early hysterectomies (at ≤ 55 years of age) are frequently performed among FPLD-affected patients. Thus, reproductive abnormalities are common among women with FPLD and necessitate careful reproductive assessment and management.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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