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Perfluorochemicals and Endometriosis *The ENDO Study*

Germaine M. Buck Louis[a], **C. Matthew Peterson**[b], **Zhen Chen**[a], **Mary L. Hediger**[a], **Mary S. Croughan**[c,d], **Rajeshwari Sundaram**[a], **Joseph B. Stanford**[e], **Victor Y. Fujimoto**[c], **Michael W. Varner**[f], **Linda C. Giudice**[c], **Anne Kennedy**[g], **Liping Sun**[a], **Qian Wu**[h,i], and **Kurunthachalam Kannan**[h,i]

[a]Divisions of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Health, Rockville, MD

[b]Division Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT

[c]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA

[d]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

[e]Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT

[f]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT

[g]Department of Radiology, University of Utah, Salt Lake City, UT

[h]Division of Environmental Health Sciences, Wadsworth Center, New York State, NY

[i]Department of Health and Environmental Health Sciences, The University at Albany, Albany, NY

Abstract

Background: Environmental chemicals may be associated with endometriosis. No published research has focused on the possible role of perfluorochemicals (PFCs) despite their widespread presence in human tissues.

Methods: We formulated two samples. The first was an operative sample comprising 495 women aged 18–44 years scheduled for laparoscopy/laparotomy at one of 14 participating clinical sites in the Salt Lake City or San Francisco area, 2007–2009. The second was a population-based sample comprising 131 women matched to the operative sample on age and residence within a 50-mile radius of participating clinics. Interviews and anthropometric assessments were conducted at enrollment, along with blood collection for the analysis of nine PFCs, which were quantified using liquid chromatography-tandem mass spectrometry. Endometriosis was defined based on surgical

Correspondence: Germaine M. Buck Louis, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Health, 6100 Executive Blvd.; Room 7B03, Rockville, MD 20852. louisg@mail.nih.gov..

visualization (in the operative sample) or magnetic resonance imaging (in the population sample). Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for each PFC (log-transformed), adjusting for age and body mass index, and then parity.

Results: Serum perfluorooctanoic acid (PFOA; OR = 1.89 [95% CI = 1.17–3.06]) and perfluorononanoic acid (2.20 [1.02–4.75]) were associated with endometriosis in the operative sample; findings were moderately attenuated with parity adjustment (1.62 [0.99–2.66] and 1.99 [0.91–4.33], respectively). Perfluorooctane sulfonic acid (1.86 [1.05–3.30]) and PFOA (2.58 [1.18–5.64]) increased the odds for moderate/severe endometriosis, although the odds were similarly attenuated with parity adjustment (OR = 1.50 and 1.86, respectively).

Conclusions: Select PFCs were associated with an endometriosis diagnosis. These associations await corroboration.

A number of persistent organic pollutants (POPs), such as dioxins, organochlorine pesticides, polybrominated diphenylethers, and polychlorinated biphenyls, have been associated with endometriosis in women.[1–5] Although many of these associations have been corroborated in experimental animals or primates at environmentally relevant concentrations for humans,[6] not all epidemiologic evidence has observed a link between POPs and endometriosis.[7–9] Reported differences focus largely on methodologic considerations such as convenience sampling, varying diagnostic approaches or self-reported disease, and varying toxicologic methods for quantifying chemical concentrations. Furthermore, methodologic complexity is introduced by the clinical “gold standard” for endometriosis, which requires visualization of disease (or its absence) by laparoscopy or laparatomy.[10] Epidemiologic investigation has been restricted primarily to women seeking clinical care, despite recognition that women identified in this way may represent only the tip of the iceberg.[11]

Noticeably absent from the evolving literature focusing on POPs and endometriosis is research on perfluorochemicals (PFCs), which comprise diverse toxic compounds that are resistant to degradation. The mean half-lives of PFCs range from 3.5 to 7.3 years,[12] allowing them to bioaccumulate in food chains and fulfill the criteria for POPs.[13] The mean PFC blood concentrations can be 20–50 times higher than polychlorinated biphenyls and 300–450 times higher than hexachlorobenzene,[14] chemical classes that have been associated with endometriosis.[3,4] We designed The Endometriosis—Natural History, Diagnosis and Outcomes (ENDO) Study to explore associations between persistent environmental chemicals and endometriosis.

METHODS

We recruited two samples of women representing women who were and were not seeking clinical care. First, the operative sample comprised women scheduled for surgery, either laparoscopy or laparotomy. This sample was matched on age and residence to women in the referent population served by the clinical facilities where the operative sample sought care. Newly diagnosed endometriosis was identified by surgical visualization in the operative sample and by pelvic magnetic resonance imaging (MRI) in the population sample. In each sample, we estimated the odds of endometriosis in relation to women’s serum chemical

concentrations. This design does not identify etiologic or causal pathways, although it does allow exploration of the relations between environmental chemicals and gynecologic disorders such as endometriosis.

The population sample was designed to represent women at risk for endometriosis and its diagnosis, in that eligible women were restricted to those who were currently menstruating and who resided within a 50-mile catchment area of participating clinical centers. We identified women in this sample through the unique Utah Population Database, which captures 94% of female Utah residents, and the white pages directory obtained from InfoUSA in California (in the absence of a State population database). Details about the methodology used for establishing both groups of women are available elsewhere.[11] The population sample underwent pelvic MRI to identify women with endometriosis who were either asymptomatic or did not seek medical care.

Ineligibility criteria were intentionally minimal irrespective of sample. Women were excluded if they had a history of surgically confirmed endometriosis (prevalent disease), were ages <18 or >44 years, had history of cancer other than nonmelanoma skin cancer, had used injectable hormones within the past 2 years, or were currently breastfeeding for 6 months or more. The operative sample comprised 495 women scheduled for laparoscopy or laparotomy irrespective of clinical indication from one of 14 participating clinical centers in and around Salt Lake City or the San Francisco Bay area. The population sample comprised 131 women who resided within the 50-mile geographic radius of participating clinical sites. The size for the operative sample was powered based on published differences for available POPs at the time of study design,[2] whereas the population sample approximated sample sizes for publications reporting associations between various POPs and endometriosis.[1–3,5] Eighty percent of eligible women participated in the study (79% in the operative and 81% in the population samples), with a 96% completion rate.

Data Collection

Women participated in baseline interviews conducted by research nurses ~2 months before surgery for the operative sample, and a similar time interval before undergoing MRI for the population sample. After the interview, standardized anthropometric assessments were performed, followed by collection of a nonfasting blood sample using equipment determined to be free of any cross-contamination with PFCs. Ongoing quality control procedures were conducted to ensure the integrity of biospecimen containers throughout the study; no contamination was found. Surgeons completed standardized postoperative data collection forms immediately after surgery to record diagnosis and severity of endometriosis using the Revised American Society for Reproductive Medicine criteria, ie, stage 1 (minimal) to stage 4 (severe).[15] All MRIs were read by two radiologists who reached diagnostic consensus. MRI has lower sensitivity and specificity for diagnosis of minimal or mild endometriosis (stages 1 and 2) in relation to the gold standard.[16] Institutional review board approval was obtained from all participating sites; women were asked to give informed consent before data collection.

PFC Analysis

We quantified nine PFCs (perfluorodecanoic acid [PFDA], perfluorohexane sulfonic acid [PFHxS], perfluorononanoic acid [PFNA], perfluorooctanoic acid [PFOA], perfluorooctane sulfonic acid [PFOS], perfluorododecanoic acid [PFDoDA], perfluoroheptanoic acid [PFHpA], perfluorooctanesulfonamide [PFOSA], and perfluoroundecanoic acid). Immediately after blood collection, samples were centrifuged, aliquoted for freezing and quantified using published standard operating procedures with high-performance liquid chromatography-tandem mass spectrometry along with an electrospray tandem mass spectrometer.[17–19] Serum samples were extracted by ion-pair extraction procedure with $^{13}C_4$-PFOS, $^{13}C_4$-PFOA, $^{13}C_2$-PFDA, and ^{13}C2-PFNA spiked as internal standards. Analyte separation was performed using an Agilent1100 series HPLC. For quantitative determination, the HPLC system was interfaced to an API 2000 triple-quadruple tandem mass spectrometer (Applied Biosystems, Foster City, CA) operated in the electrospray negative ionization mode. Instrumental parameters were optimized to transmit the $[M\text{-}K]^-$ ion before fragmentation to one or more product ions. Data were acquired by tandem mass spectrometry using multiple reaction monitoring at transitions. Quality assurance and quality control protocols include spiking of ^{13}C-labelled internal standards into each serum sample before the addition of reagents for extraction. Recoveries of $^{13}C_4$-PFOS, $^{13}C_4$-PFOA, $^{13}C_2$-PFNA, and $^{13}C_2$-PFDA were between 98% and 140%. Recoveries of native standards spiked in serum matrix were between 78% and 130%. The relative standard deviations of duplicate analyses were <5%. Milli-Q water (18 MΩ) was analyzed through the entire procedure as a procedural blank. Concentrations of PFCs in blanks were below the limit of quantification (0.1ng/ml) for all target compounds. Concentrations were recovery adjusted without substituting values below the limit of quantification to minimize bias[20,21] and are reported in ng/ml or parts per billion.

Statistical Analysis

All data were reviewed for completeness, and the distributions of PFCs were carefully assessed. Geometric means and their 95% confidence intervals (CIs) were estimated for each compound and then stratified by sample and endometriosis status. Differences were formally evaluated with either the chi-square statistic for categorical data or the Student's *t* test or Wilcoxon's nonparametric test for continuous data.

We used logistic regression to estimate the odds ratio (OR) for an endometriosis diagnosis in each sample along with corresponding 95% CIs. We estimated the odds of diagnosis because we do not know the time of disease onset. Four percent of women in each sample were excluded from analysis due to either surgical cancellations or unreadable MRIs. Separate models were run for the five PFCs with concentrations that were mostly at or above the limits of quantification (PFOS, 100%; PFOA, 98%; PFNA, 98%; PFHxS, 98%; PFDA, 85%). The remaining four PFCs had a large (63–98%) percentage of concentrations below the levels of quantification, thus precluding further analysis. All PFC concentrations were log-transformed $(1 + x)$ for analysis, and the results are presented per logarithm unit change. A priori, we defined potential confounders as including age (years) and body mass index (BMI, kg/m^2). We conducted various sensitivity analyses: (1) inclusion of parity conditional on gravidity (never pregnant, pregnant without births, pregnant with births)[22] given parity's

uncertain pathway with PFCs and endometriosis; (2) restricting endometriosis to stages 3 and 4 or moderate/severe disease in the operative sample for comparison with MRI-diagnosed endometriosis in the population sample; and (3) restricting comparison women in the operative sample to those with a primary postoperative diagnosis of a normal pelvis to remove other gynecologic pathology possibly associated with PFCs.

RESULTS

Few sociodemographic or reproductive differences were observed between the two samples, although more women were married or living as married in the operative than in the population sample (75 and 60%, respectively).[11] Fortyone percent of women in the operative sample were found to have newly diagnosed endometriosis that was skewed toward milder disease (73% stages 1–2), whereas 11% of women in the population sample had newly MRI-diagnosed endometriosis. Women in the operative sample with endometriosis were younger, leaner, and of lower parity than unaffected women (Table 1). An infertility history was the only consistent difference observed between women with and without endometriosis irrespective of sample.

Table 2 presents PFC distributions by sample and endometriosis status. There are three noteworthy trends. First, women with endometriosis were more likely to have serum PFOS, PFOA, PFNA, and PFDA concentrations in the highest tertiles relative to women without endometriosis. Second, geometric means for PFOS, PFOA, PFNA, PFDA, and PFHxS were higher for women with endometriosis in comparison with women without disease, irrespective of sample—except for PFDA in the population sample. Third, geometric means were largely comparable by disease status for PFHpA, PFDoDA, and PFOSA, irrespective of sample.

The odds of an endometriosis diagnosis were increased per logarithm unit change for PFOA (adjusted OR [AOR] = 1.89 [95% CI = 1.17–3.06]) and PFNA (2.20 [1.02–4.75]) in the operative sample when adjusting for age and BMI (Table 3). AORs remained above one per logarithm unit change when including parity conditional on gravidity in models, although point estimates were diminished (1.62 [0.99–2.66]; 1.99 [0.91–4.33], respectively). AORs remained above one per logarithm unit change with the inclusion of parity in all models except for PFHxS and PFDA in the operative and population samples, respectively (eTable; http://links.lww.com/EDE/A618).

Table 4 presents additional sensitivity analyses. When restricting endometriosis to stages 3–4, elevated AORs per logarithm unit change were observed for PFOS (1.86 [1.05–3.30]) and PFOA (2.58 [1.18–5.64]); AORs remained elevated, although point estimates were reduced after adjusting for parity (1.50 [0.82–2.74] and 1.86 [0.81–4.24], respectively). When restricting the comparison women to those with a primary postoperative diagnosis of a normal pelvis (n = 320), the AORs largely remained elevated for all PFCs, including in models adjusting for parity, with the exception of PFOS and PFHxS.

DISCUSSION

Two PFCs—PFOA and PFNA—were associated with an increased odds of an endometriosis diagnosis for the operative sample, using the clinical gold standard of surgically visualized disease (including models that adjusted for age and BMI). Adjusting for parity generally reduced the AORs, although modestly positive associations remained irrespective of sample or statistical model, with the notable exception of PFDA in the population sample. This latter observation may reflect the small size of the population group, a lower incidence of endometriosis, the use of MRI for diagnosis despite its reduced sensitivity and specificity for milder disease relative to surgical visualization,[16] or the lack of an association.

In sensitivity analyses performed with the operative sample, the AORs remained elevated (except for PFDA) when restricting endometriosis to moderate/severe disease and adjusting for age and BMI. In fact, PFOS and PFOA were associated with higher odds of diagnosis. PFOA was consistently associated with endometriosis irrespective of disease severity. However, this finding needs to be considered in the context of bidirectional errors reportedly associated with endometriosis staging, a finding we have also observed in our study.[11] When restricting the comparison women to those with a postoperative diagnosis of a normal pelvis (n = 132), a pattern of generally elevated AORs was observed. PFC concentrations were similar for women without endometriosis in the operative sample when stratified by a postoperative diagnosis of a normal pelvis versus other gynecologic pathology (data not shown), which suggests that PFCs are associated with endometriosis and not gynecologic pathology more globally. The inclusion of parity in sensitivity analyses was associated with elevated AORs for PFNA (stages 3 and 4), PFOS, and PFHxS (normal pelvis comparison group). A relatively consistent pattern of elevated AORs was observed across samples and models even with parity in the models.

Our findings should be interpreted cautiously, given the absence of comparable studies with which to weigh our findings, coupled with the exploratory nature of our work. In addition, we recognize the difficulty in specifying the correct etiologic model and have provided our results for various models consistent with a preliminary exploration. Of note is the consistent elevation of AORs across samples, even in sensitivity models adjusting for parity. This pattern could suggest that parity is a consequence rather than a determinant of endometriosis, and its adjustment may induce overadjustment bias.[23] Still, it is not currently possible to delineate the underlying etiologic pathway of endometriosis. Previous researchers have reported no association between PFC concentrations and women's age,[18,24–26] BMI, or parity[24]—all factors we considered in adjusted models. As such, the parsimonious unadjusted model may be the best fit, and our results await corroboration in future research.

The proper modeling of parity for fecundity-related outcomes is rightfully a methodologic consideration, especially for lipophilic chemicals. PFCs are not lipophilic but they do bind to serum albumin,[27] which may account for breast milk concentrations being ~1,000 times lower than blood concentrations.[24,28] In 2009, Olsen and colleagues[29] proposed that parity may induce reverse causation when assessing PFCs and fecundity outcomes such as time-to-pregnancy. Recent authors cited evidence for such reverse causation in a subset of women

from a pregnancy cohort who had live births and retrospectively reported time-to-pregnancy data.[30] However, the most heavily exposed women—those who do not achieve or maintain pregnancy—may have been systematically excluded. In addition, there could have been issues stemming from bidirectional reporting errors associated with retrospectively reported TTP.[31]

Correlations have been reported between PFCs in maternal and cord serum and also between maternal serum and breast milk, suggesting possible transplacental transfer to the fetus or lactational transfer to the infant.[32] However, the efficiency of such transfer depends on the chain length and functional group-dependent properties of PFCs,[24] and this process is less efficient than that for lipophilic chemicals. Despite some transfer, maternal serum concentrations did not change remarkably during pregnancy or through 6 months postpartum in a longitudinal study of pregnant women.[28] Moreover, the median daily uptake of PFOS and PFOA from food is estimated to be 2–3 ng/kg, with 90% coming from dietary sources,[33] underscoring the continuous nature of intake in the context of the long half-lives (3.5–8.5 years) of PFGs.[12] Our inability to delineate exposure pathways by which humans accumulate body burdens, or to identify predictors of serum PFC concentrations, reflects our as-yet-incomplete understanding of PFC toxiokinetic models and body burden.[25]

To our knowledge, this is the first article to report an association between PFCs and endometriosis. It is important to note that our findings are at concentrations below those reported in biomonitoring data for U.S. women. In addition, the magnitude of our findings for PFCs is comparable relative to other POPs such as hexachlorobenzene,[4] polychlorinated biphenyls,[2,3] and dioxin-like compounds.[1,5] Still, cautious interpretation of the findings is needed, given the exploratory nature of our work. Biological mechanisms by which PFCs might cause endometriosis remain speculative and may include estrogenic-like properties of PFCs[34]; their ability to interfere with lipid metabolism[35]; their ability to alter the hormonal milieu through pathways such as aromatase enzyme activity modulation or estrogen receptor agonism/antagonism[36]; or their ability to alter inflammatory processes, cytokine production, or adaptive and innate immune responses.[37] Recently, PFOS and PFOA were reported to be associated with a later age of pubertal maturation in a cross-sectional sample of children aged 8–18 years,[38] which is consistent with the later age of menarche reported for women with endometriosis.[39]

In summary, we found PFNA and PFOA to be associated with endometriosis at environmentally relevant concentrations. We encourage investigators with banked biospecimens to consider analyzing PFC concentrations to corroborate these novel findings. Researchers should also continue their efforts to delineate possible underlying etiologic mechanisms.

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TABLE 1

Characteristics of Samples by Endometriosis Status, Endometriosis: Natural History, Diagnosis and Outcomes Study (ENDO Study), 2007–2009 (n = 600)

	Operative Sample		Population Sample	
Characteristic	**Endometriosis (n = 190) No. (%)[a]**	**None (n = 283) No. (%)[a]**	**Endometriosis (n = 14) No. (%)[a]**	**None (n = 113) No. (%)[a]**
Age (years)				
≤24	27 (14)	33 (12)	4 (29)	25 (22)
25–29	48 (25)	55 (20)	1 (7)	22 (20)
30–34	44 (23)	58 (21)	2 (14)	18 (16)
>35	71 (37)	136 (48)	7 (50)	48 (43)
Mean (SD)	32.0 (6.8)	33.6 (7.1)	33.1 (8.1)	32.1 (7.8)
Parity				
Never pregnant	81 (43)	74 (26)	5 (36)	46 (41)
Pregnant without births	22 (11)	25 (9)	1 (7)	10 (9)
Pregnant with live births	87 (46)	182 (65)	8 (57)	57 (50)
Sought infertility treatment				
No	126 (66)	235 (83)	10 (71)	107 (95)
Yes	64 (34)	48 (17)	4 (29)	6 (5)
Body mass index (kg/m^2)				
<25.0	105 (57)	98 (35)	7 (50)	52 (48)
25.0–29.9	39 (21)	70 (25)	4 (29)	29 (27)
≥30	42 (23)	111 (40)	3 (21)	28 (26)
Mean (SD)	26.3 (7.2)	29.2 (8.4)	27.4 (9.0)	27.0 (6.7)
Current smoker				
No	170 (90)	234 (83)	13 (93)	97 (87)
Yes	20 (10)	47 (17)	1 (7)	15 (13)
Current alcohol drinking				
No	59 (47)	80 (40)	3 (38)	27 (36)
Yes	68 (54)	120 (60)	5 (63)	48 (64)
Current caffeine drinking				
No	42 (24)	47 (18)	2 (15)	41 (37)
Yes	136 (76)	218 (82)	11 (85)	71 (63)

SD indicates standard deviation.

Excludes 26 women with missing diagnostic information: 22 women in the operative sample whose surgeries were cancelled and 4 women whose MRIs were insufficient quality for diagnostic purposes.

[a]No. (%), except where indicated.

TABLE 2

Distributions of Serum Perfluorochemical Concentrations by Sample and Endometriosis Status (n = 600)

Perfluorochemicals Tertiles (ng/ml)	Operative Sample		Population Sample	
	Endometriosis (n = 190) No. (%)[a]	None (n = 283) No. (%)[a]	Endometriosis (n = 14) No. (%)[a]	None (n = 113) No. (%)[a]
PFOS				
1st (0.0300 to 5.3562)	51 (27)	105 (37)	3 (21)	44 (39)
2nd (5.3563 to 9.2455)	64 (34)	99 (35)	6 (43)	30 (27)
3rd (9.2456 to 43.2229)	75 (40)	79 (28)	5 (36)	39 (35)
Geometric mean (95% CI)	7.20 (6.55–7.91)	6.11 (5.59–6.68)	7.41 (5.17–10.63)	6.74 (5.85–7.76)
PFOA				
1st (−0.3717 to 1.8599)	49 (26)	105 (37)	4 (29)	45 (40)
2nd (1.8600 to 3.2160)	67 (35)	96 (34)	6 (43)	30 (27)
3rd (3.2161 to 9.8213)	74 (39)	82 (29)[a]	4 (29)	38 (34)
Geometric mean (95% CI)	2.65 (2.44–2.89)	2.15 (1.96–2.35)	2.49 (1.82–3.41)	2.33 (2.04–2.66)
PFNA				
1st (−0.2100 to 0.5280)	52 (27)	110 (39)	4 (29)	37 (33)
2nd (0.5281 to 0.8404)	67 (35)	91 (32)	4 (28)	37 (33)
3rd (0.8405 to 4.0996)	71 (37)	82 (29)	6 (43)	39 (35)
Geometric mean (95% CI)	0.69 (0.63–0.77)	0.58 (0.53–0.63)	0.71 (0.55–0.92)	0.64 (0.55–0.74)
PFDA				
1st (−0.0340 to 0.1523)	51 (27)	108 (38)	6 (43)	38 (34)
2nd (0.1524 to 0.2449)	65 (34)	99 (35)	3 (21)	31 (27)
3rd (0.2450 to 1.7197)	74 (39)	76 (27)	5 (36)	44 (39)
Geometric mean (95% CI)	0.20 (0.18–0.22)	0.18 (0.16–0.19)	0.17 (0.13–0.22)	0.19 (0.16–0.22)
PFHxS				
1st (0.0026 to 0.3277)	54 (28)	110 (39)	3 (21)	36 (32)
2nd (0.3278 to 0.6071)	70 (37)	86 (30)	5 (36)	38 (34)
3rd (0.6072 to 17.1021)	66 (35)	87 (31)	6 (43)	39 (35)
Geometric mean (95% CI)	0.48 (0.43–0.54)	0.43 (0.39–0.47)	0.59 (0.37–0.96)	0.51 (0.44–0.60)
PFHpA				
1st (0.0000 to 0.0307)	65 (34)	79 (28)	6 (43)	53 (47)
2nd (0.0308 to 0.0951)	56 (30)	102 (36)	4 (29)	36 (32)
3rd (0.0952 to 1.4994)	69 (36)	102 (36)	4 (29)	23 (21)
Geometric mean (95% CI)	0.05 (0.04–0.06)	0.05 (0.05–0.06)	0.03 (0.01–0.08)	0.03 (0.02–0.04)
PFUnDA				
1st (0.0001 to 0.0347)	54 (28)	94 (33)	7 (50)	48 (43)
2nd (0.0348 to 0.1199)	67 (35)	100 (35)	3 (21)	29 (26)
3rd (0.1200 to 1.5453)	69 (36)	89 (31)	4 (29)	36 (32)
Geometric mean (95% CI)	0.06 (0.05–0.08)	0.05 (0.05–0.06)	0.03 (0.01–0.08)	0.05 (0.04–0.06)
PFDoDA				
1st (0.0000 to 0.0173)	56 (30)	101 (36)	3 (21)	42 (38)

Perfluorochemicals Tertiles (ng/ml)	Operative Sample		Population Sample	
	Endometriosis (n = 190) No. (%)[a]	None (n = 283) No. (%)[a]	Endometriosis (n = 14) No. (%)[a]	None (n = 113) No. (%)[a]
2nd (0.0174 to 0.0342)	72 (38)	94 (33)	5 (36)	28 (25)
3rd (0.0343 to 0.2338)	62 (33)	88 (31)	6 (43)	42 (38)
Geometric mean (95% CI)	0.02 (0.02–0.03)	0.02 (0.02–0.02)	0.03 (0.01–0.04)	0.02 (0.02–0.03)
PFOSA				
1st (0.0000 to 0.0146)	57 (30)	95 (34)	3 (21)	48 (43)
2nd (0.0147 to 0.0311)	75 (40)	94 (33)	3 (21)	26 (23)
3rd (0.0312 to 0.0900)	58 (31)	94 (33)	8 (57)	38 (34)
Geometric mean (95% CI)	0.02 (0.02–0.02)	0.02 (0.02–0.02)	0.03 (0.02–0.04)	0.02 (0.01–0.02)

PFUnDA indicates perfluoroundecanoic acid.

Excludes 26 women with missing diagnostic information: 22 women in the operative sample whose surgeries were canceled and 4 women whose MRIs were unreadable for diagnostic purposes.

[a]No. (%), except where indicated.

TABLE 3

Perfluorochemicals and Odds of an Endometriosis Diagnosis by Sample and Model (n = 600)

Perfluorochemical (ng/ml)	Operative Sample OR (95% CI)	Population Sample OR (95% CI)	Operative Sample Adjusted[a] OR (95% CI)	Population Sample Adjusted[a] OR (95% CI)	Operative Sample Adjusted[b] OR (95% CI)	Population Sample Adjusted[b] OR (95% CI)
PFOS	1.55 (1.09–2.18)	1.23 (0.47–3.25)	1.39 (0.98–1.98)	1.29 (0.48–3.45)	1.25 (0.87–1.80)	1.37 (0.48–3.90)
PFOA	2.14 (1.34–3.43)	1.23 (0.34–4.37)	1.89 (1.17–3.06)	1.28 (0.35–4.62)	1.62 (0.99–2.66)	1.38 (0.36–5.30)
PFNA	2.75 (1.30–5.80)	1.31 (0.14–12.0)	2.20 (1.02–4.75)	1.52 (0.15–15.1)	1.99 (0.91–4.33)	1.63 (0.16–16.9)
PFDA	4.38 (1.11–17.2)	0.06 (0.00–10.7)	2.95 (0.72–12.1)	0.06 (0.00–12.3)	2.60 (0.62–10.9)	0.06 (0.00–13.3)
PFHxS	1.55 (0.82–2.95)	1.34 (0.37–4.75)	1.14 (0.58–2.24)	1.52 (0.40–5.80)	0.85 (0.42–1.73)	1.65 (0.41–6.61)

Analyses based on 473 women (excluding 26 without diagnoses) in the operative and 127 women (excluding 4 without diagnoses) in the population samples. Concentrations were log (x + 1) transformed for analysis; results are per logarithm unit change.

[a] Adjusted for age (years) and body mass index (continuous).

[b] Adjusted for age (years), body mass index (continuous), and parity conditional on gravidity (never pregnant, pregnant without births, pregnant with births).

TABLE 4

PFCs and Odds of an Endometriosis Diagnosis: Sensitivity Analyses for the Operative Sample

	Endometriosis Restricted to Stages 3 and 4 (n = 339)			Comparison Group Restricted to Postoperative Diagnosis of a Normal Pelvis (n = 320)		
PFCs (ng/ml)	OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)	OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
PFOS	1.94 (1.10–3.44)	1.86 (1.05–3.30)	1.50 (0.82–2.74)	1.40 (0.92–2.14)	1.27 (0.82–1.97)	0.94 (0.58–1.52)
PFOA	2.75 (1.26–6.02)	2.58 (1.18–5.64)	1.86 (0.81–4.24)	1.97 (1.11–3.50)	1.73 (0.96–3.10)	1.06 (0.57–2.00)
PFNA	1.45 (0.43–4.95)	1.21 (0.35–4.19)	0.99 (0.27–3.65)	2.03 (0.84–4.89)	1.56 (0.64–3.82)	1.18 (0.46–3.05)
PFDA	1.00 (0.10–10.3)	0.72 (0.06–8.09)	0.58 (0.04–7.42)	4.43 (0.80–24.4)	3.01 (0.53–17.0)	1.74 (0.28–11.0)
PFHxS	2.36 (0.97–5.76)	2.12 (0.85–5.27)	1.24 (0.47–3.31)	1.45 (0.68–3.13)	1.04 (0.46–2.35)	0.41 (0.16–1.05)

Excludes 22 women from the operative sample whose surgeries were cancelled, and 4 women from the population sample whose MRI were not readable for diagnostic purposes. Concentrations were log (x + 1) transformed for analysis; results are per logarithm unit change.

[a] Adjusted for age (continuous) and body mass index (continuous).

[b] Adjusted for age (continuous), body mass index (continuous), and parity conditional on gravity (never pregnant, pregnant without births, pregnant with births).