Title

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Journal

Fertility and Sterility, 100(1)

ISSN

0015-0282

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Publication Date

2013-07-01

DOI

10.1016/j.fertnstert.2013.03.026

Peer reviewed

Published in final edited form as:
Fertil Steril. 2013 July ; 100(1): 162–169.e2. doi:10.1016/j.fertnstert.2013.03.026.

Bisphenol A and Phthalates and Endometriosis, The ENDO Study

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Abstract

Objective—To explore the relation between bisphenol A and 14 phthalate metabolites and endometriosis.

Design—Matched cohort design.

Setting—14 clinical centers in Salt Lake City, Utah or San Francisco, California, 2007–2009.

Patients—The operative cohort comprised 495 women undergoing laparoscopy/laparotomy, while the population cohort comprised 131 women matched on age and residence.

Interventions—None

Main Outcome Measure(s)—Surgically visualized or pelvic magnetic resonance imaging (MRI) diagnosed endometriosis in the two cohorts, respectively.

Results—Odds ratios (OR) and 95% confidence intervals (CIs) were estimated using logistic regression adjusting for age, body mass index and creatinine. In the population cohort, six phthalate metabolites (mBP, mCMHP, mECPP, mEHP, mEHHP, and mEOHP) were significantly associated with approximately a twofold increase in the odds of an endometriosis diagnosis. Two phthalates were associated with endometriosis in the operative cohort when restricting to visualized and histologic endometriosis (mOP; OR=1.38; 95% CI 1.10, 1.72), or when restricting comparison women to those with a postoperative diagnosis of a normal pelvis (mEHP; OR=1.35; 95% CI 1.03, 1.78).

Conclusions—Select phthalates were associated with higher odds of an endometriosis diagnosis for women with MRI diagnosed endometriosis. The lack of consistency of findings across cohorts underscores the impact of methodology on findings.

Keywords

Bisphenol A; endometriosis; endocrine disrupting chemicals; epidemiology; phthalates

Introduction

Endometriosis is a gynecologic disorder characterized by endometrial glands and stroma that grow outside the uterine cavity. This ectopic endometrium responds to hormonal signaling and may manifest as dysmenorrhea, infertility and pain (1). While a plethora of mechanisms have been investigated, its etiology remains unknown. During the past decade, an evolving body of evidence suggests a possible role for endocrine disrupting chemicals (EDCs), which are exogenous chemicals that interfere with hormonal homeostasis including alterations in estrogen signaling (2). The Endocrine Society published a Statement on EDCs in which they noted strong evidence for adverse reproductive outcomes following exposure, including some evidence that early exposures may be associated with epigenetic changes and, possibly, trans-generational effects (3, 4). However, data gaps remain for human exposure and fecundity endpoints such as gynecologic disorders including endometriosis.

Much of the available evidence on environmental chemicals and endometriosis focuses on persistent environmental pollutants, or chemicals with long half-lives or lipophilic properties that promote their bioaccumulation and biomagnification in ecosystems and the food chain (5, 6). For example, positive associations have been reported for endometriosis and select organochlorine pesticides such as aromatic fungicides and hexachlorocyclohexane (7, 8), polychlorinated biphenyls (8–11), perfluorochemicals (12), and dioxins (13, 14). Still, other researchers have not observed relations between these chemicals and endometriosis (15, 16) underscoring remaining critical data gaps.

In contrast to the body of evidence on persistent environmental chemicals and endometriosis, limited research has focused on short lived environmental chemicals despite experimental animal evidence suggestive of reproductive and developmental toxicity (17, 18). Two such compounds - bisphenol A and phthalates – are of particular concern as possible reproductive and/or developmental toxicants including for humans as recently summarized (3). Bisphenol A (BPA) is a high production volume phenolic chemical used in the manufacture of polycarbonate plastics and epoxy resin coatings in canned food containers (19), and its widespread exposure for human populations poses important public health challenges (20). Initial controversy regarding the potential reproductive and developmental toxicity of BPA has waned given the rapidly evolving body of evidence in animals and humans suggesting adverse implications for a range of effects as recently summarized (21, 22). Given its similarity to endogenous estrogens, BPA has the ability to interact with estrogen receptors and stimulate estrogen production and also alter gonadotrophin hormone secretion (23, 24). Another emerging class of short-lived chemicals is phthalates, or so-called plasticizers since they are added to plastics to enhance flexibility and resilience (25). Like BPA, phthalates are high volume production chemicals that are metabolized quickly and excreted in urine without evidence of accumulation within the body (25–27). Phthalates produce anti-androgenic effects largely through the reduction in testosterone production and, possibly, reduced estrogen production at high doses (28, 29). Despite their relatively short half-lives, ubiquitous occurrence of BPA and phthalates may produce continual exposures for humans.

Available data on BPA and phthalates and endometriosis are emerging including five of seven human studies reporting higher phthalate concentrations in women with endometriosis than those without endometriosis (30–36), and two equivocal studies focusing on BPA (37, 38). These early studies are important contributions to the literature, but require cautious interpretation of the findings in light of important methodologic limitations including: the measurement of phthalates in plasma rather than urine (30–32; 36); self reported endometriosis (34); uncertain timing of biospecimen collection relative to timing of surgery (30–32, 35) or following surgery and diagnosis (35); categorizing women with stage 1 endometriosis with unaffected women (33, 37); and the absence of multivariable analysis to adjust for potential confounders (30–32, 37). While the findings on phthalates and BPA are intriguing, it is important to note the relatively limited number of women diagnosed with endometriosis in past research, ranging from sample sizes comprising 28 (35) to 97 women (36). In light of these suggestive data for phthalates and, to a lesser extent BPA, coupled with the continual nature of human exposure (39, 40), we analyzed banked urine samples from the Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) Study (41).

Materials and Methods

Study Design and Populations

The ENDO Study was designed with the specific aim of assessing the relation between persistent environment chemicals and endometriosis, and utilized a matched cohort design to establish both an operative and population cohort (41). All women scheduled for laparoscopy or laparotomy at one of 14 participating clinical centers in the Salt Lake City, Utah and San Francisco, California geographic areas in 2007–2009 were screened for eligibility: currently menstruating, aged 18–44 years, not breastfeeding for ≥6 months, no injectable hormonal treatment within the past two years, and no cancer history save for non-melanoma skin cancer. The operative cohort (n=495) was then matched on age and residence within a 50-mile radius to women in the surrounding geographic areas served by the clinical centers using the Utah Population Database or a telephone white pages directory for the Utah and California sites, respectively. This latter group of women comprised the population cohort (n=131) and was further screened to ensure they were at risk for endometriosis and being diagnosed, i.e., currently menstruating and residing in geographic catchment areas, respectively. Since women in the population cohort were not having surgery, they underwent standardized pelvic magnetic resonance imaging (MRI) for the assessment of endometriosis. Women with a history of surgically visualized disease or prevalent disease were ineligible for participation. *A priori* power calculations for the size of the two cohorts were based upon reported differences in concentrations of polychlorinated biphenyls by endometriosis status at the time the Study was under development (42).

Data Collection

An introductory package was mailed to all women followed by telephone screening. In-person standardized interviews were conducted with women prior to surgery or MRI followed by anthropometric assessment (43). Upon enrollment, women provided non-fasting urine (≈120 ml) samples that were collected in containers determined to be free of the chemicals under analysis. Surgeons completed standardized operative reports regarding primary and secondary diagnoses and other operative findings; endometriosis was staged using the Revised American Fertility Society's (AFS-R) classification (44). One radiologist read all MRIs using either a Siemens Avanto or Espree 1.5 Tesla scanner using a U.S. FDA approved protocol for pelvic imaging, and all diagnoses were corroborated by a second radiologist. Full human subjects' approval was awarded by all participating research institutions for the conduct of this study. Also, all participating women were provided written informed consent prior to any data collection.

Endometriosis Diagnosis

The clinical gold standard of surgically visualized disease was used to define endometriosis in the operative cohort (45, 46), and MRI visualized endometriosis for the population cohort. Disease staging (44) was only assigned for the operative cohort, given the limited sensitivity of MRIs for diagnosing minimal/mild disease (47, 48). Specifically, scores for stages 1–4 ranged from 1–5, 6–15, 16–40 and >40, respectively.

Statistical Analysis

The completeness of data and the distributions of all chemicals were assessed in the descriptive phase of research. Creatinine-adjusted geometric means along with 95% confidence intervals (CIs) were calculated then stratified by endometriosis status and cohort. Statistical significance was evaluated using the Student's t-test or Wilcoxon nonparametric test for continuous data. Logistic regression was utilized in the analytic phase to estimate the odds ratio (OR) for an endometriosis diagnosis for each chemical and by cohort along with corresponding 95% confidence intervals (CIs). Chemicals were log (x+1) transformed and standardized by their standard deviations to aid in the interpretation of the effect prior to inclusion in models. *A priori,* we defined potential confounders as: age (years), body mass index (BMI, weight in kg/height in m^2) and urinary creatinine (ng/mL). Four percent of women in each cohort were excluded from the analysis either due to surgical cancellation (n=22) or unreadable MRIs for diagnostic purposes (n=4). We conducted various sensitivity analyses for the operative cohort to assess the robustness of our findings, given remaining uncertainties about how best to model chemicals and endometriosis: 1) restricting endometriosis to stages 3 and 4 or moderate/severe disease in the operative cohort for comparison with MRI diagnosed endometriosis in the population cohort; 2) restricting endometriosis to visualized and histologically-confirmed disease; and 3) restricting the comparison women in the operative cohort to those with a primary postoperative diagnosis of a normal pelvis to minimize a possible shared etiology with other gynecologic pathology. We also re-ran adjusted models to include parity conditional on gravidity (never pregnant, pregnant without births, pregnant with births) (49), as uncertainty remains how best to model parity.

Toxicologic analysis

Fourteen phthalate metabolites were analyzed in urine (0.5 mL) samples after enzymatic deconjugation followed by solid phase extraction (50). These included: five metabolites of di (2-ethyl hexyl) phthalate (DEHP) namely, mono (2-ethyl-5-carboxyphentyl) phthalate (mECPP), mono-[(2-carboxymethyl) hexyl] phthalate (mCMHP), mono (2-ethyl-5-oxohexyl) phthalate (mEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), and mono (2-ethylhexyl) phthalate (mEHP); mono (3-carboxypropyl) phthalate (mCPP), monomethyl phthalate (mMP), monoethyl phthalate (mEP), mono (2-isobutyl phthalate) (miBP), mono-*n*-butyl phthalate (mBP), monocyclohexyl phthalate (mCHP), monobenzyl phthalate (mBzP), monoisonoyl phthalate (mNP), and monooctyl phthalate (mOP). For instrumental analysis, seven isotopically-labeled phthalate metabolites ($^{13}C_4$-mMP, $^{13}C_4$-mEP, $^{13}C_4$-mBP, $^{13}C_4$-mECPP, $^{13}C_4$-mEHP, $^{13}C_4$-mBzP, and D_4-miBP) and $^{13}C_4$-4-methylumbelliferone were used as internal standards. Total BPA concentrations were quantified using a high-performance liquid chromatography (HPLC) coupled with API 2000 electrospray triple-quadrupole mass spectrometer (51). Ongoing quality assurance and control procedures included in each batch of 25 samples a method blank, a spiked blank and a pair of matrix-spiked sample/duplicates. Trace levels of mBP, miBP, and mEHP were detected in procedural blanks (water passed through the entire analytical procedure), and sample concentrations for these compounds were subtracted from blank values. This resulted in a few negative values. The regression coefficient of calibration standards, injected at concentrations ranging from 0.05 ng/mL to 20 ng/mL, was > 0.999. The limit of

quantitation (LOQ) of phthalate metabolites and BPA was 0.1–0.5 and 0.1 ng/mL, respectively, which was determined based on the lowest point of the calibration standard and a nominal sample volume of 0.5 mL, used in this study.

Results

As previously reported, the incidence of endometriosis was 41% and 11% in the operative and population cohorts, respectively, of which 71% women in the operative cohort had minimal/mild disease (41). As Table 1 reflects, few differences were observed for study characteristics across cohorts or by endometriosis status except that affected women in the operative were significantly younger, of lower parity, leaner, and resided in smaller households than unaffected women. No significant differences were observed for these characteristics in the population cohort by endometriosis status. Table 2 reflects a pattern of higher creatinine adjusted geometric mean concentrations for all phthalates and BPA for women with than without endometriosis, but only in the population cohort. Mean differences were significantly higher for women with than without endometriosis for seven phthalates: mCPP, mBP, miBP, mECPP, mCMHP, mEHHP, and mEOHP. However, all confidence intervals overlapped for women with and without endometriosis except for mECPP (54.15; 95% CI 26.81, 109.4 and 20.7; 95% CI 17.30, 23.76, respectively), which is a major metabolite of the widely used plasticizer DEHP. No association was observed between creatinine and endometriosis (OR 1.00; 95% CI 0.82, 1.22 and OR 0.68; 95% CI 0.39, 1.20, respectively). A range of correlations was observed for each cohort between select phthalates but not with BPA (See supplemental Tables 1–2). For example, correlations ranged from 0.07 (mNP-mEP and mOP_mEP) to 0.94 (mEOHP and mECPP) in the operative cohort, and from −0.01 (mCHP_mEP) to 0.94 (mEHHP_mEOHP) in the population cohort, respectively.

Logistic regression results are presented in Table 3 and reflect no significant increased ORs for BPA or any phthalates and endometriosis in the operative cohort even after adjusting for age, BMI and creatinine. Contrarily in the population cohort, four phthalates (mECPP, mEHHP, mEOHP, and mEHP) consistently reflected approximately a 1.7 fold or higher odds of endometriosis per one standard deviation increase in concentration in unadjusted models. After adjustment, a twofold or higher increase in the odds ratios were observed for these phthalates in the population cohort. Of note, mBP and mCMHP were significantly associated with endometriosis in the population cohort, but only after adjustment (AOR=2.62; 95% CI 1.14, 6.05 and AOR=2.65; 95% CI 1.33, 5.31, respectively). Inclusion of parity in final phthalate adjusted models did not change the odds ratios in any models irrespective of cohort, except for BPA (AOR=1.97; 95% CI 1.04, 3.72) in the population cohort. Our findings were upheld when using bootstrap methods inclusive of 1,000 resamples to assess the robustness of the underlying distributional assumptions, estimated standard errors and parameters to corroborate finding, given the size of the population cohort.

Our sensitivity analyses for the operative cohort demonstrated no significant odds ratios for any of the chemicals when restricting endometriosis to stages 3–4, which we considered the closest analysis to the population cohort (Table 6). When restricting the analysis to women with visualized and histologically-confirmed disease, mOP was significantly associated with a higher odds (AOR=1.38; 95% CI 1.10, 1.72) of diagnosis. When women without endometriosis were restricted to women with a postoperative diagnosis of a normal pelvis, mEHP was significantly associated with endometriosis (AOR=1.35; 95% CI 1.03, 1.78) corroborating the significant association seen in the population cohort.

Discussion

We found a positive association for 6 of 14 phthalate metabolites quantified for study purposes reflecting a twofold or higher increased odds of endometriosis per one standard deviation increase in concentration. However, the findings were only observed in the population cohort where endometriosis was diagnosed from pelvic MRIs. Of note is the consistency of findings when implementing bootstrapping techniques aimed at assessing the robustness of the underlying distributional assumptions. Our findings are at chemical concentrations that are lower than those reported for women in the 2007–2008 NHANES biomonitoring data, except for mMP, mCPP and mEHP that were higher in one or both of our cohorts. Complete exposure data are readily available online for the NHANES Survey (52).

We observed mEHP to be the only phthalate consistently associated with endometriosis across cohorts, though significance was only achieved when disease was restricted to comparison women with a normal pelvis in the operative cohort. Also of note is the observation that three of the phthalate metabolites (mECPP, mEHHP, mEOHP) associated with endometriosis are derived from the parent compound di-(2-ethylhexyl)-phthalate (DEHP), which is the most widely used phthalate and is present in cosmetics and other personal care products that are a source of continual human exposure (40). When summing DEHP metabolites (mECPP, mCMHP, mEHHP, mEOHP, and mEHP), a higher odds of endometriosis remained for the population cohort (AOR=2.81; 95% CI1.42, 5.56). Considerable caution is needed in considering this finding, given the relatively high degree of correlation for select metabolites that argues against simple summing of concentrations. Three previous studies reported higher concentrations of DEHP in women with than without endometriosis in unadjusted comparisons (30, 31, 36). Also, women with the null GSTMI genotype and higher urinary concentrations of Σ mEHP were reported to have a higher odds of adenomyosis and leiomyomas but not endometriosis than women with lower concentrations and the wild type (35), suggesting a possible role for various gynecologic diseases. Unfortunately, we do not have genetic data available in the ENDO Study. Recent experimental evidence using mice revealed that increasing doses of DEHP compromised endometrial receptivity and the number of implantation sites (53) suggesting a possible adverse effect on the endometrium or hormonal signaling.

The relation between BPA and endometriosis was less evident in the population cohort and only emerged as significant when adjusting for parity along with other relevant covariates. If endometriosis and parity share a common origin, its adjustment may induce overadjustment bias yielding a spurious finding (54). As such, we did not observe a relation between BPA and endometriosis corroborating an earlier study (37) but failing to offer support for the endometriosis-like phenotype reported for female offspring of BPA exposed mice (55).

While speculative, an etiologic association between phthalates and endometriosis is plausible via three possible pathways: 1) EDCs may induce gene expression by acting as hormones or disrupting metabolism or synthesis of endogenous hormones; 2) EDCs may affect the nervous system and alter signaling of the endocrine system; or 3) EDCs may induce epigenetic changes through alterations in transcriptional capabilities (56). A remaining challenge is in determining the onset of endometriosis, particularly with increasing speculation regarding an early origin for female fecundity and gynecologic health (57). This hypothesis acknowledges that uterine endometrial gland development begins *in utero* and is completed during puberty in humans (58), and that early disruptions in signaling before puberty may result in altered adult morphology and function. The exact timing of endometriosis onset remains unknown, as are the determinants associated with its progression or regression across the window of reproductive age.

Our findings are strengthened by the novel study design that utilized both an operative and population cohort from which we can assess the robustness of findings, and the quantification of chemicals in urine rather than plasma or serum. Because of the short-lived nature of phthalates in human bodies, measurement of parent phthalates in plasma or serum risks contamination arising during sample collection and/or analysis. Specifically, serum enzymes are reported to hydrolyze DEHP to mEHP during storage (59, 60). We believe that measurement of phthalate metabolites in urine provides better estimate of exposures than measurement of parent compounds in serum/plasma, as was done in some earlier studies. Our findings might be limited by the collection of urine samples across women's menstrual cycles, though recent evidence suggests no relation between menstrual cycle phase and urinary BPA concentrations (61). The ENDO Study was originally powered to detect differences in persistent organochlorine concentrations and endometriosis, and not specifically BPA or phthalates. The confidence intervals provide sufficient precision required for meaningful interpretation of model parameters increasing our confidence in the observed findings. We are unaware of such research focusing on phthalate concentrations across the menstrual cycle. Given our inability to identify women at risk for endometriosis prior to the onset of symptoms or diagnosis, our findings are limited by the relatively short interval between quantification of urinary chemicals and diagnosis. Other study limitations include our inability to detect endometriosis stages 1–2 in the population cohort, given the limited sensitivity (69%) and specificity (75%) of MRI for detecting milder disease relative to histologically confirmed disease (46). However, MRI diagnosis is reported to be excellent for endometriomas that correspond to stages 3 and 4 (62, 63). Despite errors associated with MRI diagnosed endometriosis relative to the clinical gold standard of visualization, the blinding of surgeons and radiologists to women's chemical concentrations argues against biases.

Other important limitations include the exploratory nature of our analysis including the potential for non-monotonic responses that may be relevant for EDCs and human health (64) and our relatively crude attempt to assess mixtures in keeping with the nature of human exposure by summing metabolites. We remain perplexed by the inconsistency of findings by cohort and have been unable to identify unique differences in women that may have manifested in effects largely limited to the population cohort. Possible explanations may include limited power for detection of effects in the operative cohort apart from sensitivity analyses, or selection biases arising from the sampling frameworks or enrollment sites used for study. None-the-less, our findings underscore the importance of study design and methodology in the interpretation of human health effects.

Continual research aimed at delineating the relation between environmental endocrine disrupting chemicals and gynecologic disorders such as endometriosis is paramount, and an important step for addressing larger data gaps regarding global concerns about declining female fecundity (65, 66) and endometriosis' association with later onset diseases such as autoimmune disorders and cancer (67, 68). We urge the continued design of novel research with innovative methodologies for investigating the relation between environment and endometriosis at the population level.

Acknowledgments

Funding: Funded by the Intramural Research Program, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health (contracts NO1-DK-6-3428; NO1-DK-6-3427; 10001406-02). The Ethicon Endo-Surgery, Inc., donated the HARMONIC® ACE 36P scalpel blades for use in the study through a signed Materials Transfer Agreement with the University of Utah and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

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Table 1

Mean comparison of cohorts by endometriosis status, The ENDO Study (n=600).

Characteristic	Operative Cohort (n=473)		Population Cohort (n=127)	
	Endometriosis N=190 Mean (±SD)	None N=283 Mean (±SD)	Endometriosis N=14 Mean (±SD)	None N=113 Mean (±SD)
Age at menarche (years)	13.0 ± 1.8	12.8 ± 1.6	13.2 ± 1.5	12.7 ± 1.5
Age at enrollment (years)	32.0 ± 6.8 *	33.6 ± 7.1	33.1 ± 8.3	32.1 ± 7.8
Menstrual cycle length (days)	28.1 ± 8.7	31.6 ± 31.7	27.4 ± 3.5	30.3 ± 11.1
Parity (# live births)[a]	1.8 ± 1.3 *	2.2 ± 1.4	2.6 ± 1.6	2.2 ± 1.5
Body mass index (kg/m^2)	26.3 ± 7.2 **	29.2 ± 8.4	27.4 ± 9.0	27.0 ± 6.7
Household size (# persons)	3.2 ± 1.5 **	3.7 ± 1.7	3.5 ± 1.9	3.7 ± 1.9

NOTE: Excludes 22 women in the operative cohort whose surgeries were cancelled and 4 women in the population cohort whose MRIs were unreadable.

SD, denotes standard deviation

[a]Restricted to 394 gravid women.

*P<0.05;

**P<0.01 comparison of endometriosis status within cohort

Fertil Steril. Author manuscript; available in PMC 2014 July 01.

Table 2

Geometric mean comparison of urinary phthalate and bisphenol A by cohort and endometriosis status, ENDO Study, 2005–2009 (n=600).

Chemicals	Operative Cohort (n=473)		Population Cohort (n=127)	
	Endometriosis N=190 # (%)	None N=283 # (%)	Endometriosis N=14 # (%)	None N=113 # (%)
Phthalates (ng/mL)				
mMP (range 0.003–93.865)				
Geometric mean (95% CI)	2.12 (1.71, 2.62)	2.35 (2.03, 2.72)	3.67 (1.80, 7.47)	2.71 (2.14, 3.44)
mEP (range 3.075–1202.4)				
Geometric mean (95% CI)	107.2 (88.73, 129.4)	109.6 (93.64, 128.3)	152.0 (59.11, 390.8)	138.2 (107.1, 178.4)
mCPP (range 0.001–99.653)				
Geometric mean (95% CI)	2.71 (2.29, 3.22)	3.41 (3.02, 3.84)	5.75 (3.38, 9.80)	4.06 (3.41, 4.83) *
mBP (range −4.683–572.068)				
Geometric mean (95% CI)	12.07 (10.67, 13.66)	11.01 (10.02, 12.10)	19.13 (12.53, 29.22)	11.24 (9.74, 12.97) *
miBP (range −11.931–365.692)				
Geometric mean (95% CI)	7.28 (6.39, 8.30)	6.82 (6.16, 7.55)	13.32 (7.67, 23.15)	7.59 (6.37, 9.05) **
mECPP (range 1.874–1196.57)				
Geometric mean (95% CI)	24.68 (21.31, 28.60)	24.98 (22.23, 28.07)	54.15 (26.81, 109.4)	20.27 (17.30, 23.76) **
mCMHP (range 2.401–698.372)				
Geometric mean (95% CI)	29.34 (25.46, 33.81)	29.19 (25.92, 32.88)	53.54 (25.93, 110.5)	22.51 (19.00, 26.66) *
mEHHP (range 0.042–796.609)				
Geometric mean (95% CI)	16.34 (13.68, 19.53)	14.40 (12.51, 16.56)	32.37 (11.97, 87.53)	11.86 (9.83, 14.32) *
mEOHP (range 0.4480–599.763)				
Geometric mean (95% CI)	10.98 (9.37, 12.86)	10.12 (8.90, 11.50)	23.03 (9.85, 53.84)	8.29 (6.86, 10.02) *
mCHP (range 0.001–81.903)				
Geometric mean (95% CI)	0.03 (0.03, 0.04)	0.04 (0.03, 0.04)	0.04 (0.02, 0.08)	0.03 (0.02, 0.04)
mBzP (range −0.390–338.335)				
Geometric mean (95% CI)	6.96 (6.10, 7.94)	7.82 (6.98, 8.76)	9.85 (5.96, 16.27)	6.46 (5.33, 7.84)
mEHP (range −19.865–224.851)				

Chemicals	Operative Cohort (n=473)		Population Cohort (n=127)	
	Endometriosis N=190 # (%)	None N=283 # (%)	Endometriosis N=14 # (%)	None N=113 # (%)
Geometric mean (95% CI)	4.75 (3.78, 5.97)	4.12 (3.40, 5.01)	8.32 (4.00, 17.28)	3.07 (2.09, 4.49) **
mOP (range 0.000–56.639)				
Geometric mean (95% CI)	0.06 (0.05, 0.07)	0.06 (0.05, 0.07)	0.06 (0.03, 0.11)	0.05 (0.04, 0.07)
mNP (range 0.004–52.380)				
Geometric mean (95% CI)	0.16 (0.13, 0.18)	0.16 (0.14, 0.18)	0.22 (0.11, 0.46)	0.16 (0.12, 0.21)
BPA (ng/mL):				
Range (−1.802–497.966)				
Geometric mean (95% CI)	1.45 (1.14, 1.84)	1.66 (1.40, 1.97)	4.19 (2.18, 8.03)	1.65 (1.23, 2.23) **
Creatinine (mg/dL):				
Range (9.130–488.600)				
Geometric mean (95% CI)	87.85 (78.83, 97.89)	89.39 (81.85, 97.62)	57.21 (35.50, 92.21)	79.03 (68.03, 91.80)

NOTE: Excludes 22 women in the operative cohort whose surgeries were cancelled, and 4 women in the population cohort whose MRIs were unreadable. Phthalates and BPA concentrations were standardized by creatinine only for the calculation of geometric means for comparison purposes and rounded to three decimal places.

P-values compare geometric means for women with and without endometriosis for each cohort:

* P<0.05,

** P<0.01

CI, denotes 95% confidence interval

Table 3

Phthalates and bisphenol A and the odds of an endometriosis diagnosis by cohort and model, ENDO Study, 2007–2009 (n=600).

Chemicals	Operative Cohort (n=473)	Population Cohort (n=127)	Operative Cohort (n=473)	Population Cohort (n=127)	Bootstrap Method (n=127)
	OR (95% CI)	OR (95% CI)	AOR[a] (95% CI)	AOR[a] (95% CI)	AOR
Phthalates					
mMP	1.00 (0.84, 1.21)	0.96 (0.55, 1.69)	0.98 (0.78, 1.24)	1.25 (0.66, 2.37)	1.39 (0.68, 2.86)
mEP	0.97 (0.81, 1.17)	0.87 (0.49, 1.54)	1.01 (0.82, 1.24)	1.07 (0.56, 2.04)	1.19 (0.51, 2.40)
mCPP	0.83 (0.69, 1.01)	1.05 (0.60, 1.82)	0.78 (0.63, 0.98)	1.27 (0.71, 2.26)	1.33 (0.63, 2.36)
mBP	1.08 (0.90, 1.30)	1.23 (0.70, 2.15)	1.11 (0.86, 1.43)	**2.62 (1.14, 6.05)**	**3.61 (1.17, 11.0)**
miBP	1.02 (0.85, 1.22)	1.35 (0.72, 2.56)	1.02 (0.80, 1.29)	2.22 (0.98, 5.04)	3.26 (0.99, 10.2)
mECPP	0.98 (0.81, 1.17)	**1.78 (1.02, 3.11)**	0.99 (0.79, 1.25)	**2.92 (1.46, 5.84)**	**3.53 (1.54, 8.07)**
mCMHP	0.99 (0.82, 1.19)	1.56 (0.89, 2.73)	0.98 (0.77, 1.26)	**2.65 (1.33, 5.31)**	**3.34 (1.25, 8.27)**
mEHHP	1.09 (0.91, 1.31)	**1.74 (1.03, 2.92)**	1.10 (0.89, 1.36)	**2.20 (1.23, 3.94)**	2.61 (0.99, 6.23)
mEOHP	1.05 (0.87, 1.26)	**1.70 (1.00, 2.88)**[b]	1.06 (0.85, 1.32)	**2.33 (1.26, 4.29)**	**2.65 (1.15, 5.50)**
mCHP	1.08 (0.89, 1.30)	0.63 (0.09, 4.57)	1.07 (0.87, 1.32)	0.74 (0.23, 2.45)	1.89 (0.16, 4.02)
mBzP	0.89 (0.74, 1.08)	1.04 (0.60, 1.80)	0.84 (0.65, 1.07)	1.47 (0.76, 2.85)	1.63 (0.75, 3.28)
mEHP	1.18 (0.97, 1.44)	**2.18 (1.05, 4.56)**	1.20 (0.97, 1.49)	**2.59 (1.17, 5.75)**	**3.06 (1.60, 6.22)**
mOP	1.03 (0.86, 1.23)	0.79 (0.25, 2.53)	1.06 (0.87, 1.29)	0.84 (0.40, 1.78)	0.97 (0.003, 3.95)
mNP	0.86 (0.69, 1.07)	0.91 (0.48, 1.72)	0.85 (0.68, 1.06)	0.90 (0.50, 1.63)	0.90 (0.40, 1.54)
BPA	0.93 (0.77, 1.12)	1.62 (0.93, 2.80)	0.96 (0.79, 1.19)	1.68 (0.96, 2.92)	**1.82 (1.01, 3.36)**

NOTE: Concentrations were log transformed and rescaled by their standard deviations for analysis. Significant ORs in boldface.

[a]AOR adjusted for age (years), BMI (continuous) and creatinine (continuous).

[b]CI before rounding (1.0002, 2.8769)

CI, denotes 95% confidence interval; OR, odds ratio.

Table 4

Phthalates and bisphenol A and the odds of an endometriosis diagnosis – sensitivity analyses for operative cohort (n=339).

Sensitivity Model	Endometriosis Diagnosis Stages 3 and 4 (n=339)		Visualized & Histologically-Confirmed Endometriosis (n=473)		Comparison Women with Post-Operative Diagnosis Normal Pelvis (n=320)	
Chemicals	**OR (95% CI)**	**AOR[a] (95% CI)**	**OR (95% CI)**	**AOR[a] (95% CI)**	**OR (95% CI)**	**AOR[a] (95% CI)**
Phthalates:						
mMP	1.09 (0.81, 1.47)	1.18 (0.81, 1.72)	1.09 (0.85, 1.41)	1.08 (0.78, 1.50)	1.01 (0.81, 1.26)	0.99 (0.75, 1.31)
mEP	0.99 (0.74, 1.31)	1.04 (0.75, 1.43)	1.04 (0.80, 1.34)	1.04 (0.78, 1.39)	1.00 (0.80, 1.24)	1.05 (0.81, 1.35)
mCPP	0.83 (0.61, 1.12)	0.83 (0.59, 1.16)	0.90 (0.69, 1.18)	0.86 (0.63, 1.18)	0.82 (0.66, 1.03)	0.75 (0.57, 0.99)
mBP	0.98 (0.74, 1.30)	1.04 (0.71, 1.53)	0.98 (0.76, 1.27)	0.91 (0.64, 1.31)	1.10 (0.88, 1.38)	1.13 (0.84, 1.52)
miBP	0.93 (0.71, 1.24)	0.96 (0.67, 1.38)	1.08 (0.83, 1.41)	1.08 (0.77, 1.51)	1.05 (0.84, 1.32)	1.09 (0.82, 1.46)
mECPP	0.89 (0.66, 1.20)	0.91 (0.63, 1.33)	1.02 (0.79, 1.33)	1.03 (0.75, 1.42)	1.09 (0.87, 1.38)	1.18 (0.87, 1.60)
mCMHP	0.91 (0.68, 1.21)	0.91 (0.62, 1.34)	1.02 (0.78, 1.32)	0.98 (0.70, 1.38)	1.10 (0.87, 1.38)	1.14 (0.84, 1.55)
mEHHP	0.97 (0.72, 1.30)	0.99 (0.71, 1.38)	1.06 (0.82, 1.37)	1.03 (0.77, 1.38)	1.26 (0.99, 1.60)	1.32 (1.01, 1.75)
mEOHP	0.95 (0.71, 1.27)	0.98 (0.69, 1.39)	1.08 (0.84, 1.39)	1.08 (0.79, 1.46)	1.19 (0.94, 1.51)	1.27 (0.95, 1.70)
mCHP	1.21 (0.95, 1.55)	1.24 (0.93, 1.65)	1.02 (0.80, 1.30)	1.00 (0.78, 1.28)	1.01 (0.83, 1.23)	0.99 (0.81, 1.21)
mBzP	0.82 (0.61, 1.10)	0.77 (0.52, 1.14)	1.01 (0.78, 1.31)	1.02 (0.72, 1.42)	0.89 (0.71, 1.11)	0.79 (0.59, 1.07)
mEHP	1.20 (0.88, 1.63)	1.23 (0.88, 1.72)	1.22 (0.93, 1.61)	1.21 (0.90, 1.62)	**1.35 (1.05, 1.74)**	**1.35 (1.03, 1.78)**
mOP	1.12 (0.88, 1.43)	1.16 (0.89, 1.50)	**1.30 (1.05, 1.60)**	**1.38 (1.10, 1.72)**	0.97 (0.79, 1.19)	0.99 (0.80, 1.22)
mNP	0.99 (0.77, 1.29)	0.99 (0.76, 1.28)	0.94 (0.70, 1.26)	0.93 (0.70, 1.25)	0.84 (0.65, 1.09)	0.84 (0.64, 1.11)
BPA	0.91 (0.67, 1.23)	0.94 (0.68, 1.28)	0.93 (0.71, 1.22)	0.94 (0.71, 1.26)	1.11 (0.87, 1.40)	1.21 (0.93, 1.58)

NOTE: All chemicals were log transformed then rescaled by their standard deviations for analysis. Significant ORs in boldface.

[a]AOR adjusted for age (years), BMI (continuous) and creatinine (continuous).

CI, denotes 95% confidence interval; OR, odds ratio