RESEARCH PAPER

Impact of Environmental Endocrine Disruptors on Menstrual and Ovulatory Dysfunction: A Population Based Exposure Response Study

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ABSTRACT

OBJECTIVE:

To assess the population level exposure-response relationship between environmental endocrine disruptors (EEDs) and the occurrence of menstrual and ovulatory dysfunction.

METHODS AND MATERIALS:

A population based cohort study was conducted on 14 community health districts in the form of a prospective cohort. The number of reproductive-age women (18-42 years) that were recruited was 3,842 through stratified random sampling. Adjusted odds ratios (aORs) in multivariable logistic regression and restricted cubic spline models were fitted using exposure quartile to predict adjusted odds ratios at different levels of exposure, age, BMI, parity, socioeconomic status, contraceptive history, smoking, and comorbid endocrine conditions. P = 0.05 was selected as the statistical significance.

RESULTS:

34.7% and 28.9% of the subjects had shown menstrual and ovulatory dysfunction respectively. A graded exposure-response relationship was observed for total phthalate metabolites (aOR 2.14, 95% CI 1.68–2.73, $p < 0.001$) and PFAS (aOR 1.89, 95% CI 1.45–2.46, $p < 0.001$) with menstrual irregularity. Stratified analyses showed the modulation of effects by BMI and age with women aged 28-35 years and with BMI >25 kg/m² being more susceptible to the effects.

CONCLUSION:

There is a dose-dependent association between population-level exposure to EEDs and risk of menstrual and ovulatory dysfunction. Such results highlight the importance of EED biomonitoring in community reproductive health screening and gynecological diagnostic algorithms, and the need to have policies in place that aim to reduce exposures on the part of the population.

KEYWORDS: Endocrine disruptors, menstrual dysfunction, ovulatory dysfunction, population based study, exposure to environmental factors.

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INTRODUCTION

Menstrual and ovulatory dysfunction is a significant worldwide public health challenge with a prevalence of about 25-35 percent of women of reproductive age in various socioeconomic and geographical regions.[1,2] These disorders are clinically characterized by cycle irregularity, oligomenorrhea, amenorrhea, excessive menstrual bleeding, dysmenorrhea and anovulation or oligo-ovulation, which all lead to poor fertility, heightened risk of endometrial pathology, metabolic dysregulation and poor health-related quality of life.[3,4] Menstrual and ovulatory disturbances have in the past been attributed to dysregulation of hypothalamic-pituitary-ovarian (HPO) axis, polycystic ovary syndrome (PCOS), thyroid disorders, hyperprolactinemia, severe stress, nutritional deficiencies, and genetic factors.[5,6] Nevertheless, recent epidemiological data is increasingly pointing the blame of pertinent environmental agents, especially environmental endocrine disruptors (EEDs) as contributors to the disruption of the reproductive cycle, which is modifiable.[7,8]

EEDs are a heterogeneous group of synthetic and natural chemicals, which have the ability to disrupt hormonal signaling, receptor binding, steroidogenesis, and epigenetic regulation of reproductive tissues.[9] The phthalates, bisphenol A (BPA), par- and polyfluoroalkyl substances (PFAS), organochlorine pesticides, parabens, and some heavy metals are typical examples of EEDs that are routinely examined. These substances are common in consumer products, food packaging, water systems and agricultural runoff as well as indoors, and the human exposure of these substances is found in nearly all populations. Mechanistically, EEDs disrupt endocrine homeostasis via several mechanisms: estrogenic or anti-estrogenic receptor signaling, androgen receptor signaling, interference with thyroid hormones, interference with kisspeptin-GnRHpulsatility and direct toxicity to ovarian granulosa and theca cells.[10,11] Recent experimental and translational research has shown that chronic exposure to low dose of EEDs can modulate follicular recruitment, oocyte maturation, luteal progesterone synthesis, and cause endometrial receptivity defects. Although well-supported by biological plausibility, there exists a body of disjointed evidence on the association between levels of quantified EED exposure and clinically defined menstrual and ovulatory dysfunction, and most studies are based on self-reported menstrual symptoms, small biomarker panels, or cross-sectional studies that lacked exposure-response modeling.[12]

This study intends to produce evidence that will facilitate the integration of environmental health surveillance with clinical reproductive medicine by using stratified community recruitment, LC-MS/MS biomonitoring, standardized gynecological phenotyping and advanced statistical modeling. The results should be used to inform primary care screening guidelines, gynecological diagnosis algorithms, environmental exposure guidelines, and policy frameworks that can be used to promote environmental equity in reproductive care in environmentally-burdened populations.

MATERIALS AND METHODS

This study utilised a combination of a population-based prospective cohort design and cross-sectional exposure-outcome assessment. It has been carried out in 14 community health districts and done in collaboration with the primary care networks, community reproductive health clinics, and tertiary gynecology centers. The geographic catchment was made up of urban, peri-urban and rural areas to make sure that there was heterogeneity in environmental exposure and also socialeconomic diversity. Population and Sampling Reproductive-age women (18-42 years old) met the criteria of being not pregnant at baseline and having not had hysterectomy, as well as having not used hormonal contraceptives within 90 days before study date. The exclusion criteria were known malignancies, uncontrolled thyroid or adrenal diseases, being in lactation and taking systemic endocrine treatment. The stratified multistage random sampling was used in which the primary unit of sampling was district, secondary was community health centers and tertiary was age stratified registries. An odds ratio of 1.5 in the highest quartile of exposure was determined to determine the appropriate sample size of 3,800, considering a baseline prevalence of 30, power of 80,

alpha =0.05, and attrition of 15%. The enrollments were done in March 2023 to February 2024 and the participation rate was 81.4. The exposure to endocrine disruptors was measured in the first-morning spot urine and fasting serum samples at the baseline visits. Bisphenol A (BPA), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-2-ethylhexyl phthalate (MEHP) and mono-isononyl phthalate (MiNP) were all considered urinary biomarkers. As one of the markers of historical exposure to organochlorine, serum biomarkers were used, such as perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHxS), and hexachlorobenzene (HCB). Samples were handled within 2 hours, kept at -80C and subjected to liquid chromatography-tandem mass spectrometry (LC-MS/MS) procedures that were in accord with the CDC/WHO environmental biomonitoring guidelines (29,30). Outcome Assessment Menstrual dysfunction was assessed by use of standardized 90 days menstrual tracking calendar, validated clinical interview and a gynecological examination. The dysfunctions were categorized as: (1) irregular cycles (greater than 7 days per 3 or more cycles), (2) amenorrhea (greater than 90 days without bleeding), (3) heavy menstrual bleeding (greater than 80 mL per cycle by pictorial blood assessment chart) and (4) dysmenorrhea necessitating analgesic therapy (VAS greater than 6/1 The ovulatory dysfunction was established through mid-luteal serum progesterone (day 21 with a variance of 2 in 28 days), transvaginal ultrasound follicular tracking (no dominant follicle rupture 18 mm), and luteal phase length (less than 10 days). Serum hormone panels (FSH, LH, estradiol, progesterone, AMH, prolactin and TSH) were measured by chemiluminescent immunoassay. Gynecological assessment was done on the participants by obstetrician-gynecologists board certified and blinded, as to exposure status.

The concentration of EED in the statistic was grouped into quartiles by the distribution of population. Primary analyses used multivariate logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of menstrual and ovulatory dysfunction by exposure quartile with the lowest quartile being a reference. The model is restricted cubic spline (4 knots) used to measure non-linear dose-response relationships. Interaction terms were tested according to the effect modification by age, BMI and socioeconomic status. To test the robustness, sensitivity analyses were done with no participants with PCOS, thyroid disorders or high stress scores. Missing data (<5% were treated using multiple imputation (m=10). R v4.3.2 and SAS v9.4 were used to make analyses. $p < 0.05$ was used to determine statistical significance. Age, BMI, parity, SES, smoking, history of contraceptives, diet, stress and comorbid endocrine conditions were all adjusted in all models.

RESULTS

The mean age was 29.4 ± 5.6 years, mean BMI 24.8 ± 4.3 kg/m², and 62.3% resided in urban or peri-urban zones. A total of 1,290 participants (34.7), and 1,075 (28.9) were found to have menstrual and ovulatory dysfunction, respectively.

There is a definite graded exposure response relationship between total urinary phthalate metabolites and menstrual dysfunction. The odds ratio of menstrual irregularity were found to be 2.14 times higher in participants in the highest exposure quartile than in the lowest quartile regardless of age, BMI, SES and contraceptive history. The statistically significant trend (p of trend = 0.001) confirms the use of phthalates as the alterable risk factors to disrupt the cycle among populations in communities.

Table 1. Adjusted Odds Ratios and Prevalence of Menstrual Dysfunction by Quartiles of Total Phthalate Metabolites.

Quartile	N	Prevalence (%)	aOR (95% CI)	p-value
Q1 (Ref)	929	24.1	1.00	–
Q2	931	31.6	1.42 (1.12–1.79)	0.004
Q3	928	38.4	1.78 (1.41–2.25)	<0.001
Q4	930	44.8	2.14 (1.68–2.73)	<0.001

BPA and PFAS have both been shown to have dose-dependent relationships with ovulatory dysfunction. The outermost quartiles give a 76 and 89 percent higher odds of anovulation, respectively.

Table 2. Adjacent Odds ratios of Ovulatory Dysfunction by BPA and PFAS exposure Quartiles

Analyte	Quartile	aOR (95% CI)	p-value
BPA	Q1	1.00	–
	Q2	1.28 (1.04–1.57)	0.019
	Q3	1.51 (1.22–1.87)	0.001
	Q4	1.76 (1.32–2.35)	0.002
PFAS	Q1	1.00	–
	Q2	1.34 (1.09–1.65)	0.006
	Q3	1.62 (1.31–2.00)	<0.001
	Q4	1.89 (1.45–2.46)	<0.001

The statistically significant monotonic relationship between legacy organochlorine and heavy menstrual bleeding is observed. The threshold effect develops in the third quartile, which suggests that there are cumulative bioaccumulation effects on the endometrial vascularization and the regulation of prostaglands.

Table 3. Organochlorine Pesticide and Heavy Menstrual Bleeding Exposure-Response Modeling.

HCB Quartile	N Cases	aOR (95% CI)	p-value	Trend p
Q1	112	1.00	–	<0.001
Q2	134	1.21 (0.94–1.56)	0.132	
Q3	168	1.48 (1.15–1.91)	0.002	
Q4	201	1.64 (1.21–2.22)	0.001	

The curve of risk has non-linear spline modeling, which shows an increasing risk curve after the 50 th percentile of cumulative EED exposure.

Table 4. Limited Cubic Spline Regression of the Total EED burden and Anovulation risk.

EED Index Percentile	Adjusted OR (95% CI)	p-value
10th	0.94 (0.82–1.08)	0.381
30th	1.12 (1.01–1.25)	0.038
50th	1.38 (1.24–1.53)	<0.001
70th	1.74 (1.52–1.99)	<0.001
90th	2.21 (1.81–2.69)	<0.001

The adiposity and age effect modification suggests that women with a higher BMI and in their prime reproductive age (2835) are more vulnerable. The adipose tissue is probably an EED reservoir, which extends a half-life and enhances endocrine interference.

Table 5. Stratified: menstrual dysfunction in relation to stratified analysis by BMI and age: interaction effects.

Subgroup	High Exposure aOR (95% CI)	p-value	Interaction p
BMI <25 kg/m²	1.82 (1.41–2.35)	<0.001	0.014
BMI ≥25 kg/m²	2.47 (1.89–3.22)	<0.001	
Age 18–27	1.91 (1.42–2.57)	<0.001	0.021
Age 28–35	2.38 (1.76–3.21)	<0.001	
Age 36–42	1.64 (1.18–2.27)	0.003	

DISCUSSION

This is a population-based exposure-response study that shows that environmental endocrine disruptors biomarkers have a statistically significant, dose-dependent relationship with clinically validated menstrual and ovulatory dysfunction. The results are consistent with the new literature on reproductive toxicology and build on previous data with community-based recruitment, standardized gynecological phenotyping and advanced exposure-response modeling. The best association was observed with total phthalate metabolites which had a 2.14-fold higher odds in the highest exposure quartile. BPA and PFAS showed strong dose-response curves with anovulation whereas legacy organochlorine pesticides showed significant associations with heavy menstrual

bleeding. The stratified analyses showed the effect modification by BMI and age emphasizing the importance of adipose bioaccumulation and age-related ovarian weakness.

Mechanistic studies have provided biological plausibility of these associations by showing that phthalates interfere with the aromatase activity of granulosa cells, disrupt estrogen synthesis and change the dynamics of the GnRH pulse generator.[13,14] BPA has been shown to compete with estradiol at the nuclear receptor, stimulate abnormal endometrial gene expression and lead to oxidative stress in ovarian follicles (33). PFAS disrupt transport of thyroid hormones, reduce the amplitude of luteinizing hormone surges, and disrupt corpus luteum.[15] Organochlorine pesticides are estrogenic and anti-androgenic, have effects on prostaglandin metabolism and endometrial decidualization.[16] These findings have far reaching implications on primary care and community health infrastructure in terms of community medicine. Menstrual and ovulatory dysfunction have often been undiagnosed in the community as cycle irregularity is normalized, access to specialized gynecological evaluation is limited and environmental exposure screening is not available.[17,18] The inclusion of EED biomonitoring as part of a regular reproductive health assessment might allow the detection of potentially endangered groups of people in advance, especially in those areas where the presence of environmental pollution or high-intensity use of plastics/PFAS was reported. The exposure literacy, dietary modification, and household product substitution community health worker training programs have shown preliminary effectiveness in alleviating loads of biomarkers.[19,20] Population-level reproductive dysfunction could be alleviated by scaling such interventions in primary care networks, and environmental health equity would be improved.

The exposure-response model used in the present study fills a gap in the environmental reproductive epidemiology. Previous studies have mostly been based on categorical exposure comparisons or linear assumptions that can render biological thresholds or non-linear processes obscure.[21,22] Our spline analysis indicates that the risk curve is accelerating beyond the median levels of exposure, indicating that population-wide mitigation policies should focus on reducing exposure of high-percentile groups, and not on equal mitigation. It is consistent with the precautionary principle of environmental health where the greatest benefits of protection on disproportionately exposed subpopulations have disproportionate benefits on the general population in terms of human health.[23] BMI and age interaction effects also indicate that community medicine has a need to be fine-tuned, with intensity of screening and intervention focusing on the susceptibility profiles of individuals.

Overall, this paper offers strong population-based data that environmental endocrine disruptors play a major role in causing menstrual and ovulatory dysfunction as a result of linear exposure-response interactions. The results fill the gap between community medicine surveillance and gynecological clinical practice and recommend that environmental exposure assessment be an integral part of the reproductive health assessment. EED mitigation measures should be included in public health programs, primary health care guidelines and gynecological practices to ensure integrity of the reproductive cycle and equity in environmental health.

CONCLUSION

The exposure to environmental endocrine disruptors is statistically significant and dose-dependent with menstrual and ovulatory dysfunction in a population based cohort. Phthalates, BPA, PFAS, and organochlorine pesticides all cause clinically proven disruption of the menstrual cycle and anovulation, and are more likely to cause disruption in women with high BMI and those aged 28-35 years. These results highlight the need to incorporate EED biomonitoring and exposure reduction into the community reproductive health screening and

gynecological diagnosis models. Primary care guidelines and environmental controls should put exposure reduction at the forefront of the public health policy, to protect reproductive health equity. **REFERENCES**

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