Fine particulate matter and polycystic ovarian morphology

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Abstract

Background: Polycystic ovary morphology (PCOM) is an ultrasonographic finding that can be present in women with ovulatory disorder and oligomenorrhea due to hypothalamic, pituitary, and ovarian dysfunction. While air pollution has emerged as a possible disrupter of hormone homeostasis, limited research has been conducted on the association between air pollution and PCOM.

Methods: We conducted a longitudinal cohort study using electronic medical records data of 5,492 women with normal ovaries at the first ultrasound that underwent a repeated pelvic ultrasound examination during the study period (2004–2016) at Boston Medical Center. Machine learning text algorithms classified PCOM by ultrasound. We used geocoded home address to determine the ambient annual average PM2.5 exposures and categorized into tertiles of exposure. We used Cox Proportional Hazards models on complete data (n = 3,994), adjusting for covariates, and additionally stratified by race/ethnicity and body mass index (BMI).

Results: Cumulative exposure to PM2.5 during the study ranged from 4.9 to 17.5 µg/m³ (mean = 10.0 μg/m³). On average, women were 31 years old and 58% were Black/African American. Hazard ratios and 95% confidence intervals (CI) comparing the second and third PM2.5 exposure tertile vs. the reference tertile were 1.12 (0.88, 1.43) and 0.89 (0.62, 1.28), respectively. No appreciable differences were observed across race/ethnicity. Among women with BMI ≥ 30 kg/m², we observed weak inverse associations with PCOM for the second (HR: 0.93, 95% CI: 0.66, 1.33) and third tertiles (HR: 0.89, 95% CI: 0.50, 1.57).

Conclusions: In this study of reproductive-aged women, we observed little association between PM2.5 concentrations and PCOM incidence. No dose response relationships were observed nor were estimates appreciably different across race/ethnicity within this clinically sourced cohort.

Keywords: Polycystic ovary morphology (PCOM), Air pollution, Fine particulate matter, Electronic medical records

Background

Polycystic ovary morphology (PCOM) is an ultrasonographic finding that can be present in women with ovulatory disorder and oligomenorrhea due to hypothalamic, pituitary, and ovarian dysfunction [1–3]. PCOM may be seen in multiple endocrine states where follicular development is altered, resulting in arrested antral follicles [4]. PCOM has been observed in about 30–50% of patients with functional hypothalamic amenorrhea [5–7] and is more common in women with Cushing’s disease [8]. Women with polycystic ovary syndrome (PCOS), a disease notable for oligomenorrhea and androgen excess, and PCOM have demonstrated higher risks of insulin resistance, dyslipidemia and cardiovascular diseases compared to women with only PCOS [9]. The clinical significance of PCOM alone is undefined as previous literature on direct health impacts of PCOM remains sparse. However, some studies have observed...
associations between PCOM and elevated anti-Müllerian hormone (AMH) among healthy girls with regular menses [10], as well as a higher severity of primary dysmenorrhea [11].

Air pollution has emerged as a possible disrupter of hormone homeostasis interfering with the female reproductive system [12, 13]. Epidemiologic studies have begun to evaluate specific reproductive health outcomes in relation to environmental air pollution including infertility [14–17], hormone function [18, 19], and menstrual cycle status [20–22]. Likewise, animal studies have investigated associations between ovarian function and air pollution, finding significant decreases in the area occupied by primordial follicles for mice exposed to pollutants from diesel exhaust [23] and changes in AMH levels for mice exposed to fine particulate matter (PM$_{2.5}$) [24]. However, there is a dearth of research on the association between PM$_{2.5}$ and PCOM. One study to date has evaluated PM$_{2.5}$ and PCOS, rather than PCOM [25], and observed an increased risk of PCOS with higher levels of PM$_{2.5}$ [25]. However, this study assessed air pollution one year before diagnosis without investigating potentially longer windows of exposure and diagnosed PCOS via ICD-9-CM codes [25].

In the current study, we investigated the association between PM$_{2.5}$ and PCOM in a population of reproductive-age women receiving clinical care. Women in our study had a minimum of four years of exposure data prior to diagnosis. We hypothesized that higher levels of PM$_{2.5}$ would be associated with increased incidence of PCOM.

**Methods**

**Study population**

This study was conducted at Boston University Medical Campus (BUMC), an academic research medical center in Boston, Massachusetts which includes Boston University School of Medicine (BUSM) and Boston Medical Center (BMC). BMC is the largest safety-net hospital in New England. Greater than 50% of BMC patients come from underserved populations that depend on government coverage for health expenses through programs like Medicare, Medicaid, and the Health Safety Net [26]. In 2009, 34.4% of the population treated at BMC was White, 31.5% was Black and 17.6% was Hispanic/Latino [27].

The BUMC and BUSM Institutional Review Board approved the protocol. Using electronic medical records (EMR) data, we identified patients who attended outpatient clinic visits as described by Cheng et al. [28]. Briefly, all pelvic ultrasounds from October 1, 2003 through December 12, 2016 were retrieved from the BMC Clinical Data Warehouse (CDW) for women of reproductive age (i.e., between 18 and 45 years old), excluding women with a previous diagnosis of endocrinopathy noted by the following ICD-9 codes and descriptions: 182.0 Malignant neoplasm of corpus uteri, except isthmus; 240.0 Simple Goiter; 240.9 Goiter unspecified; 241.0 Nontoxic multinodular goiter; 241.1 Nontoxic multinodular goiter; 242 Thyrotoxicosis with or without goiter; 243 Congenital hypothyroidism, 244 Acquired hypothyroidism; 245 Thyroiditis; 246 Other disorders of thyroid; 255.0 Cushing Syndrome; 255.1 Hyperaldosteronism; 255.2 Adrenogenital disorders; 255.3 Other corticoadrenal overactivity; 255.4 Corticoadrenal insufficiency; 255.5 Other adrenal hypofunction; 255.6 Medulloadrenal hyperfunction; 255.8 Other specified disorders of adrenal glands; 255.9 Unspecified disorders of adrenal glands; 256.8 Other ovarian dysfunction, in order to determine incidence of PCOM among healthy participants without this previous diagnosis. This process yielded 25,535 unique patient IDs [28]. The time period for data query corresponds to the entire period when ICD-9 coding was in use at BUMC.

**Study design: longitudinal cohort approach**

We applied a longitudinal cohort approach using the EMR derived dataset. We identified women undergoing an initial and follow-up transvaginal pelvic ultrasound who received care from 2004–2016 and lived in Massachusetts during this timeframe. Patients were followed through 2016, the last year that air pollution data was available. The first pelvic ultrasound examination over the study period was designated as the initial visit. To establish that women were at risk of PCOM but free of this condition at initial visit, we included only women who had normal ovaries as assessed by the first ultrasound (n=5,492). Follow-up pelvic ultrasound examinations determined the incidence of PCOM.

**Exposure assessment: measurement of fine particulate matter PM$_{2.5}$**

We estimated ambient annual average PM$_{2.5}$ using the North American PM$_{2.5}$ model based on the combination of aerosol optical depth (AOD) measurements, the chemical transport model (GEOS-Chem) and geographically weighted regression results, as previously described [29]. Briefly, geophysical PM$_{2.5}$ estimates were consistent with those of globally distributed monitors on the ground ($R^2=0.81$; slope = 0.90). Geographically weighted regression was also used to account for the residual bias of monitors, producing higher cross validated agreement with ground monitors ($R^2=0.90–0.92$; slope = 0.90–0.97) [29]. The PM$_{2.5}$ model yields annual average PM$_{2.5}$ concentration estimates globally at 1 × 1 km resolution, and results are compiled in a freely available database (https://sites.wustl.edu/acag/datasets/surface-pm2-5/#V4.NA.03). These AOD measurements are available at high temporal resolution and provide a
historical repository that can be used to retrospectively model PM$_{2.5}$ [30–34]. Annual average PM$_{2.5}$ exposure data starting in the year 2000 were matched to geocoded home addresses from the patient’s initial visit using Esri ArcPro version 2.2 and SAS v. 9.4.

**Outcome assessment: diagnosis of PCOM**
We used the novel technique of identifying PCOM or polycystic ovaries based on radiologic report data as described previously using the Rule Based Classifier Model based on the Rotterdam criteria [2, 28]. Briefly, an ovary was defined as “PCOM-present” if there were 12 or more 2–9 mm follicles in each ovary and/or if ovarian volume was greater than 10 mL without the presence of confounding pathology [2, 28, 35–37]. Confounding pathology included presence of a dominant follicle (>10 mm), corpus luteum, abnormal cyst, or ovarian asymmetry, in which case further investigation would be warranted. If a) confounding pathology occurred, b) an ovary was not measured, c) the radiologic ultrasound was not mentioned, or d) PCOM was recorded as absent, we categorized the ultrasound as showing no indication of PCOM and compared this population to patients who had a “PCOM-present” diagnosis.

**Covariates**
We extracted EMR information from the patient’s initial visit on demographic characteristics, including age, race/ethnicity, marital status, educational attainment, and smoking status. We calculated body mass index (BMI kg/m$^2$) from the height and weight abstracted from this visit. If data on these variables were not available from the initial visit, they were obtained from the visit most proximate to the initial visit within the 2004–2015 timeframe. We restricted our analysis to women with BMIs between 19–54 kg/m$^2$ [38], as values outside of this range were not verified and were likely related to documentation errors. Calendar year denoted the year of annual average PM$_{2.5}$ measurement. There were 3,994 women with complete data included in the analysis.

**Statistical analysis**
We described the characteristics of the study population using proportions, means and standard deviations. As PM$_{2.5}$ concentrations were measured yearly, we utilized time-varying Cox proportional hazards models to examine the association between PM$_{2.5}$ and the incidence of PCOM. Women contributed person-years starting from January 2000 until ultrasound detected PCOM or the last ultrasound visit. The first pelvic ultrasound examination during the study period confirmed that the patient was free of PCOM at the initial visit. Patients were able to contribute 4 to 15 years of person-time for follow-up. To account for patterns in pollution over time (Figure S1), all models were stratified by age in years and calendar year within the Cox model and were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We categorized air pollution exposure into tertiles in our main analysis to allow for non-linearity and to account for extreme values. The lowest tertile (tertile 1) was designated as the reference group. We conducted multivariate analyses with covariates hypothesized to be associated with air pollution and with PCOM based on a priori literature and directed acyclic graphs [39] (Figure S2). These models included race/ethnicity, educational attainment, marital status, and smoking status [40–44], with educational attainment and marital status serving as proxies for socioeconomic status/household income. We evaluated patients with complete information on all covariates, PM$_{2.5}$ based on complete data on geocoded home address, and PCOM ($n = 3,994$). To evaluate if the association between PM$_{2.5}$ and PCOM varied by BMI and race/ethnicity, we conducted stratified analyses by these variables. As a sensitivity analysis, we also evaluated 1) women who never moved over the study period ($n = 682$) to determine the impact of possible exposure misclassification due to residential mobility and 2) continuous air pollution models to assess precision without categorical restrictions.

**Results**
At initial visit, mean age was 31.1 years among the 3,994 women in the analysis (Table 1). The majority of women were Black/African American (57.9%), never smokers (73.5%), and not married (75.2%). About one-third of women graduated high school or received their GED (32.7%) and about one-quarter attained education beyond high school (27.7%). Mean BMI at initial visit was 30 kg/m$^2$. Mean PM$_{2.5}$ level from 2004–2016 was 10.0 µg/m$^3$, over the entire study period (Table 1).

HRs comparing the second and third tertiles to the reference (first) tertile were 1.12 (95% CI: 0.88, 1.43) and 0.89 (95% CI: 0.62, 1.28), respectively (Table 2, Fig. 1). Thus, we did not observe a dose–response relationships across tertiles. Among women with a BMI $<$ 30 kg/m$^2$, HRs comparing the second and third tertiles to the reference tertile were 1.30 (95% CI: 0.91, 1.88) and 0.89 (95% CI: 0.53, 1.49), respectively (Table 3). Among women with BMI $\geq$ 30 kg/m$^2$, we observed weak inverse associations with PCOM for both the second (HR: 0.93, 95% CI: 0.66, 1.33) and third (HR: 0.89, 95% CI: 0.50, 1.57) tertiles when compared to the reference tertile (Table 3, Fig. 1). When stratified by race/ethnicity, the HRs (95% CI) between PM$_{2.5}$ and PCOM among Black, Hispanic/ Latino and White women comparing the third tertile to the reference tertile were 0.73 (95% CI: 0.44, 1.20), 0.93
Discussion

In this population of women who attended clinic visits at BMC, long-term PM$_{2.5}$ concentrations were not appreciably associated with incidence of PCOM. We observed associations that were inconsistent in direction across tertiles, with no evidence of a dose response relationship. We also found little variation in estimates across race/ethnicity categories, and slight variations across BMI categories, though estimates were imprecise.

Previous studies evaluating the association between air pollution and women’s reproductive health outcomes have been limited. A study of 133 Polish women of reproductive age found that higher concentrations of PM$_{10}$, as measured by municipal-level monitoring data, were associated with luteal phase shortening; however, the study did not observe any effect on follicular phase or overall cycle length [45]. A time-series analysis from northwestern China recorded more than 51,893 outpatient visits for menstrual disorders and found that higher short-term ambient PM$_{10}$ concentrations were associated with more outpatient visits for menstrual disorders, with a stronger effect observed among females aged 18–29 years [46]. Furthermore, a cross-sectional study of 34,832 women from the Nurses’ Health Study II observed an association between average total suspended particles with increased odds of androgen excess irregularity phenotypes and lengthened time to cycle regularity [22]. However, none of these studies investigated PCOM explicitly, nor did they assess exposure to fine particulate matter.

Although there is no previous research on air pollution and PCOM, one prior study by Lin et al. has evaluated the relationship between fine particulate matter and PCOS. This prospective Taiwanese study observed
that exposure to PM$_{2.5}$ at the fourth (34.78–67.45 ppb) vs. first quartile (22.49–27.23 ppb) was associated with a 3.56-fold increased risk of PCOS (95% CI: 3.05–4.15) [25]. While the investigators examined PCOS diagnosed with ICD-9 CM codes, they were able to evaluate PM$_{2.5}$ concentrations one year before diagnosis but did not have a longer follow-up, which may have overlooked part of the relevant exposure window within this population. Furthermore, Lin et al. were not able to evaluate effects at lower levels of exposure that are more common in the United States and other countries (mean and 90th percentile weighted annual average across U.S. trend sites in 2019: 7.7, 9.5 µg/m$^3$) [47] or to assess the potential for a threshold effect, given the relatively high PM$_{2.5}$ concentrations in the cohort (mean ± standard deviation daily concentrations of PM$_{2.5}$: 30.9±6.2 µg/m$^3$). Our study has been able to fill a gap in the literature by specifically evaluating the association between long-term PM$_{2.5}$ and PCOM more commonly observed at lower levels of exposure.

Limitations of the current study include possible restricted generalizability. Our study was limited to women receiving care at BMC and who had an indication for repeated pelvic ultrasounds. Additionally, our EMR dataset was not designed as a traditional

Table 3 Association of fine particulate matter (PM$_{2.5}$) (in exposure tertiles) and Polycystic Ovarian Morphology, by BMI status (< 30 vs. > = 30 kg/m$^2$) $^a$ (n = 3788)

| PM 2.5 (µg/m$^3$) | < 30 kg/m$^2$ | > = 30 kg/m$^2$ |
|-------------------|---------------|-----------------|
|                   | # Cases | HR (95% CI) | # Cases | HR (95% CI) |
| 5.10–9.70         | 441     | Reference     | 5.0–9.70 | Reference   |
| 9.80–11.30        | 171     | 1.30 (0.91, 1.88) | 9.80–11.30 | 134 | 0.93 (0.66, 1.33) |
| 11.40–14.80       | 35      | 0.89 (0.53, 1.49) | 11.40–17.50 | 26 | 0.89 (0.50, 1.57) |

$^a$ Stratified by age in years and calendar year in the Cox model; Adjusted for race, education, marital status, smoking status

Table 4 Association of tertile fine particulate matter (PM$_{2.5}$) exposure and Polycystic Ovarian Morphology, by race/ethnicity $^a$

| PM 2.5 (µg/m$^3$) | Black/African American | Hispanic/Latino | White | Other |
|-------------------|-------------------------|-----------------|-------|-------|
|                   | n = 2336 | n = 204 | n = 610 | n = 190 |
| 4.90–9.70         | Reference | Reference | Reference | Reference |
| 9.80–11.30        | 0.97 (0.72, 1.33) | 0.80 (0.20, 3.27) | 0.99 (0.51, 1.90) | 1.12 (0.87, 1.43) |
| 11.40–17.50       | 0.73 (0.44, 1.20) | 0.93 (0.14, 5.90) | 0.60 (0.23, 1.59) | 0.83 (0.58, 1.19) |

$^a$ Stratified by age in years and calendar year; Adjusted for education, marital status, smoking status; Displaying categories for those that self-identified as Black/African America, Hispanic Latino, and White or as another race/ethnicity – 16.5% of participants declined to answer and were not included in this analysis

- Fig. 2 PM2.5 and incidence of PCOM, stratified by race. Adjusted for education, marital status, smoking status. Model stratified by age in years and calendar year. Categories shown for medical record recorded race/ethnicity with highest proportions. Displaying categories for those that self-identified as Black/African America, Hispanic Latino, and White.

that exposure to PM$_{2.5}$ at the fourth (34.78–67.45 ppb) vs. first quartile (22.49–27.23 ppb) was associated with a 3.56-fold increased risk of PCOS (95% CI: 3.05–4.15) [25]. While the investigators examined PCOS diagnosed with ICD-9 CM codes, they were able to evaluate PM$_{2.5}$ concentrations one year before diagnosis but did not have a longer follow-up, which may have overlooked part of the relevant exposure window within this population. Furthermore, Lin et al. were not able to evaluate effects at lower levels of exposure that are more common in the United States and other countries (mean and 90th percentile weighted annual average across U.S. trend sites in 2019: 7.7, 9.5 µg/m$^3$) [47] or to assess the potential for a threshold effect, given the relatively high PM$_{2.5}$ concentrations in the cohort (mean ± standard deviation daily concentrations of PM$_{2.5}$: 30.9±6.2 µg/m$^3$). Our study has been able to fill a gap in the literature by specifically evaluating the association between long-term PM$_{2.5}$ and PCOM more commonly observed at lower levels of exposure.

Limitations of the current study include possible restricted generalizability. Our study was limited to women receiving care at BMC and who had an indication for repeated pelvic ultrasounds. Additionally, our EMR dataset was not designed as a traditional
prospective cohort study since EMR and air pollution data were both collected before the start of our investigation. However, we were able to assess those at risk of PCOM by only including women with normal ovaries at the first ultrasound visit and at least one repeated pelvic ultrasound examination thereafter to determine development of PCOM. Furthermore, we were unable to confirm if women received care and/or ultrasound examinations at another facility during the timeframe of this analysis. We therefore may not have been able to precisely assess the time to PCOM diagnosis for these women, if, for instance, diagnosis occurred prior to their subsequent ultrasound at BMC. The number of ultrasounds that women underwent and the time between each ultrasound was also not uniform across women. Since PCOM may not cause acute symptoms that indicate an immediate ultrasound, and as women were not screened for PCOM at regular intervals for detection, women may have contributed person time after PCOM occurred but before PCOM was detected via ultrasound. We additionally did not have information accessible to link PM$_{2.5}$ to address changes over time. Consequently, the participant’s address at the initial visit was used to assess PM$_{2.5}$ concentration. Nevertheless, our findings were comparable to results for the entire analytic sample when we restricted our sample to those that had not moved addresses throughout the study. Furthermore, we could not expand our study further to other pollutants in addition to PM$_{2.5}$ because geocoded data on these other components were not available at the time of our analysis.

For this hospital sourced radiological data, ultrasound assessment was not timed to menstrual cycle day, which was also a limitation in our study as we were not able to account for influence of cycle day on ultrasound imaging [48, 49]. However, this study does not evaluate antral follicle count (AFC) measurements on the basal phase of the menstrual cycle (cycle day 2–4), as it was not designed to evaluate AFC in relation to PCOM [50, 51].

Given the age of the population (mean: 31.1; standard deviation: 7.6), we suspect within person variation to be deviation: 7.6), we suspect within person variation to be

greater than the 95% CI: 96.5, 98.5%) when comparing machine learning text algorithm used for classification of PCOM in pelvic ultrasounds based on the radiographic report compared to the hand-labeled test set [28]. However, misclassification of the outcome may have occurred if some providers did not report the necessary information
to characterize PCOM, or if there were discrepancies in ultrasound reading by the technician. We also observed marginal inverse associations among women with obesity (BMI $\geq 30$ vs. $< 30$ kg/m$^2$) for both higher level tertiles compared to the reference tertile. Yet, results suggesting a potential reduction in incidence of PCOM among obese women may be due to detection bias, as pelvic examinations may be less sensitive for detecting PCOM among obese women.

Additionally, we defined our detection of PCOM based on Rotterdam criteria. Recently, alternative criteria have been proposed including a higher follicle threshold (≥ 25 follicles per ovary), but the sensitivity of these criteria is still being considered [50, 52]. To add further complexity, women with regular menstrual cycles can be defined as having PCOM in the setting of very robust ovarian reserve or younger age [53]. A previous study found the prevalence of polycystic ovaries assessed by antral follicle count to be 32% and that prevalence decreased with age [53]. Future studies should focus on the dynamic aspects of ovarian physiology in an unselected population and include measures of ovarian volume, follicle counts in the basal phase of the menstrual cycle corresponding to follicular recruitment, and include cycle length in the analysis, rather than focusing of PCOM alone.

Although the EMR dataset did not permit us to conduct a traditional prospective cohort study, a strength of our analysis was that we were able to assess those at risk of PCOM over time by having access to baseline and follow-up data. We included women with normal ovaries at the first ultrasound visit and at least one repeated pelvic ultrasound examination thereafter to determine incidence of PCOM. Furthermore, to our knowledge, this is the first study to evaluate exposure to fine particulate matter in relation PCOM. Additional strengths include the efficiency of this analysis in integrating retrospective air pollution assessment in evaluation of reproductive disease pathophysiology. Furthermore, the rich set of EMR data provided a large sample size of nearly 4,000 women and the ability to control for important confounding variables.

Conclusions

Among a population of reproductive-age women receiving clinical care within our cohort, PM$_{2.5}$ concentrations were generally not associated with higher risk of PCOM at the fine particulate matter levels within our cohort. No dose response relationships were observed nor were estimates appreciably different across race/ethnicity. Future studies with greater variation in exposure levels and additional data on ovarian physiology in unselected populations would further extend these findings.
Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12940-022-00835-1.

Additional file 1: Table S1. Association of tertile fine particulate matter (PM2.5) and Polycystic Ovarian Morphology (n=682) among those participants that never moved. Table S2. Association of quartile fine particulate matter (PM2.5) exposure and Polycystic Ovarian Morphology (complete analysis, continuous). Figure S1. PM2.5 Cumulative Average by Year, averaged across participants (2003-2016). Figure S2. Directed Acyclic Graph used to identify covariates for inclusion in regression models as confounding variables. Note: Figure generated using DAGitty v2.3 (Textor and Hardt 2011). Abbreviations: SES, socioeconomic status; PM2.5, fine particulate matter.

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Authors’ contributions
VF—analysis, interpretation, and manuscript writing. JC—code developments to processing Census data, and the Washington University in Saint Louis support in assembling the clinical dataset and Pratik Shingru for his contributions.

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Authors’ contributions
VF—analysis, interpretation, and manuscript writing. JC—code development and output to obtain PCOM data from patient medical records, major contributor in editing the manuscript. KL—provided fine particulate matter and address data, interpretation, major contributor in editing the manuscript. AA—methodology, interpretation, major contributor in editing the manuscript. SM concept, interpretation, major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality agreements and the privacy of individuals within the electronic medical records data.

Declarations
Ethics approval and consent to participate
The BUMC and BUSM Institutional Review Board approved the protocol.

Consent for publication
Not Applicable.

Competing interests
The authors have no conflicts of interest to declare.

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References
1. Laven JSE, Imani B, Eijkemans MJC, Fauser BCJM. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynecol Surv. 2002;57(11):755–67.
2. RotterdamESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
3. Mikhail S, Punjala-Patel A, Gavrilova-Jordan L. Hypothalamic-Pituitary-Ovarian Axis Disorders Impacting Female Fertility. Biomedicines. 2019;7(1):5.
4. Pigny R, Merlen E, Robert Y, Cortej-Rudelli C, Decanter C, Jonard S, et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. J Clin Endocrinol Metab. 2003;88(12):5957–62.
5. Futterweit W, Yeh HC, Mechanick JJ. Ultrasoundographic study of ovaries of 19 women with weight loss-related hypothalamic oligo-amenorrhea. Biomed Pharmacother Biomedicine Pharmacother. 1988;42(1):279–83.
6. Schachtier M, Balen AH, Patel A, Jacobs HS. Hypogonadotropic patients with ultrasonographically detected polycystic ovaries: endocrine response to pulsatile gonadotropin-releasing hormone. Gynecol Endocrinol. 1996;10(5):327–35.
7. Sum M, Warren MP. Hypothalamic amenorrhea in young women with underlying polycystic ovary syndrome. Fertil Steril. 2009;92(6):2106–8.
8. Kalskas GA, Korbonits M, Isidori AM, Webb JA, Trainer PJ, Monson JP, et al. How common are polycystic ovaries and the polycystic ovarian syndrome in women with Cushings syndrome? Clin Endocrinol (Oxf). 2000;53(4):493–500.
9. Inan C, Karadag C. Correlation between ovarian morphology and biochemical and hormonal parameters in polycystic ovary syndrome. Pak J Med Sci. 2016;32(3):742–5.
10. Villarroel C, Merino PM, López P, Eyzaguirre FC, Van Velzen A, Iiugetz G, et al. Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Mullerian hormone. Hum Reprod Off Engl. 2011;26(10):2861–8.
11. Jeong JY, Kim MK, Lee I, Yun J, Won YB, Yun BH, et al. Polycystic ovarian morphology is associated with primary dysmenorrhea in young Korean women. Obstet Gynecol Sci. 2016;59(3):29–34.
12. Goldman M, Troisi R, Rexrode K. Women and Health [Internet]. 2nd Edition. Academic Press. Cited 2021 Feb 16. Available from: https://www.elsevier.com/books/women-and-health/goldman/978-0-12-384978-6
13. Rudel RA, Perovich LJ. Endocrine disrupting chemicals in indoor and outdoor air. Atmospheric Environ Off Engl 1994. 2009;43(1):170–81.
14. Boulet SL, Zhou Y, Shliber J, Kissin DM, Strosnider H, Shin M. Ambient air pollution and in vitro fertilization treatment outcomes. Hum Reprod Off Engl. 2019;02(34(10):2036–43.
15. Carré J, Gatieml N, Moreau J, Pinnaud J, Leandri R. Influence of air quality on the results of in vitro fertilization attempts: A retrospective study. Eur J Obstet Gynecol Reprod Biol. 2017;210:116–22.
16. Noble J, Schisterman EF, Ha S, Buck Louis GM, Sherman S, Mendola P. Time-varying cycle average and daily variation in ambient air pollution and fecundability. Hum Reprod Off Engl. 2018;01;33(1):166–76.
17. Mahalingaiah S, Hart JE, Laden F, Farland LV, Hewlett MM, Chavarro J, et al. Adult air pollution exposure and risk of infertility in the Nurses Health Study II. Hum Reprod Off Engl. 2016;31(3):638–47.
18. La Marca A, Spaggiari G, Domiccoi D, Grassi R, Casonati A, Balardi E, et al. 2020. Elevated levels of nitrous dioxide are associated with lower AMH levels: a real-world analysis. Hum Reprod [Internet]. Cited 2020 Oct 30. Available from: https://academic.oup.com/humrep/article-advance-publish/doi/https://doi.org/10.1093/humrep/deaa214/5909140
19. Tomei G, Carrozza M, Fortunato BR, Capozzella A, Ciarrocca M, Fortunato BR, et al. Exposure to traffic pollutants and effects on 17-beta-estradiol (E2) in female workers. Int Arch Occup Environ Health. 2006;80(1):70–7.
20. Giosqui-Allemand L, Thalabard JC, Rosetta L, Siroux V, Bouyer J, Slama R. Can atmospheric pollutants influence menstrual cycle function? Environ Health Perspect. 2002;110:13605.
21. Liang Z, Xu C, Fan Y, Liang Z-Q, Kan H-D, Chen R-J, et al. Association between air pollution and menstrual disorder outpatient visits: A time-series analysis. Ecotoxicol Environ Saf. 2020;192:110283.
22. Mahalingaiah S, Missmer SE, Cheng JJ, Chavarro J, Laden F, Hart JE. Perimenarchal air pollution exposure and menstrual disorders. Hum Reprod Off Engl. 2018;01;33(3):512–9.
23. Ogliari KS, Lichtenfels AJ de FC, de Marchi MR, Ferreira AT, Dohnhoff M, Saldiva PHV. Intratracheal exposure to diesel exhaust diminishes adult ovarian reserve. Fertil Steril. 2013;99(6):1681–8.

24. Gai HF, An J-X, Qian X-Y, Wei Y-J, Williams JP, Gao G-L. Ovarian Dangers Produced by Aerosolized Fine Particulate Matter (PM2.5) Pollution in Mice: Possible Protective Medications and Mechanisms. Chin Med J (Engl). 2017;130(12):1400–10.

25. Lin S-Y, Yang Y-C, Chang CY-Y, Lin C-C, Hsu W-H, Ju S-W, et al. 2019. Risk of Polycystic Ovary Syndrome in Women Exposed to Fine Air Pollutants and Acidic Gases: A Nationwide Cohort Analysis. Int J Environ Res Public Health. Cited 2020 Oct 30. 16(23). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6296786/.

26. Boston Medical Center. 2021. About Us | Boston Medical Center [Internet]. Cited 2021 May 20. Available from: https://www.bmc.org/about-us

27. Boston Medical Center. Boston Medical Center Race and Ethnicity Profiles. 2021. About Us | Boston Medical Center [Internet].

28. Cheng JJ, Mahalingaiah S. 2019. Data mining polycystic ovary morphology in electronic medical record ultrasound reports. Fertil Res Pract [Internet]. Cited 2020 Aug 31. S. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6886166/.

29. Hammer MS, van Donkelaar A, Li C, Lyapustin A, Sayer AM, Hsu NC, et al. Global Estimates and Long-Term Trends of Fine Particulate Matter Concentrations (1998–2018). Environ Sci Technol. 2020;54(13):7879–90.

30. Di Q, Kloo K, Kourakis P, Lyapustin A, Wang Y, Schwartz J. Assessing PM2.5 exposures with High Spatiotemporal Resolution across the Continental United States. Environ Sci Technol. 2016;50(9):4712–21.

31. Donkelaar A van, Martin RV, Park RJ. Estimating ground-level PM2.5 using aerosol optical depth determined from satellite remote sensing. J Geophys Res Atmospheres [Internet]. 2006 [cited 2020 Aug 21];11(11D21). Available from: https://agupubs.onlinelibrary.wiley.com/doi/abs/https://doi.org/10.1029/2005JD006996

32. Kloo K, Kourakis P, Coull BA, Lee HJ, Schwartz J. Assessing temporally and spatially resolved PM 2.5 exposures for epidemiological studies using satellite aerosol optical depth measurements. Atmos Environ. 2011;45:6267–75.

33. van Donkelaar A, Martin RV, Brauer M, Hsu NC, Kahn RA, Levy RC, et al. Global Estimates of Fine Particulate Matter using a Combined Geophysical-Statistical Method with Information from Satellites, Models, and Monitors. Environ Sci Technol. 2016;50(7):3762–72.

34. van Donkelaar Aaron, Martin Randall V, Brauer M, Boys Brian L. Use of Satellite Observations for Long-Term Exposure Assessment of Global Concentrations of Fine Particulate Matter. Environ Health Perspect. 2015;123(2):135–43.

35. Balen A. Ovulation induction for polycystic ovary syndrome. Hum Fertil. 2000;3(2):106–11.

36. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: is it worth counting the follicles? Hum Reprod. 2003;18(3):598–603.

37. Pache TD, Vladimiroff JW, Hop WC, Fauser BC. How to discriminate between normal and polycystic ovaries: transvaginal US study. Radiology. 2000;213(2):365–72.

38. van Donkelaar Aaron, Martin Randall V, Brauer M, Boys Brian L. Use of Satellite Observations for Long-Term Exposure Assessment of Global Concentrations of Fine Particulate Matter. Environ Health Perspect. 2015;123(2):135–43.

39. Balen A. Ovulation induction for polycystic ovary syndrome. Hum Fertil. 2000;3(2):106–11.

40. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: is it worth counting the follicles? Hum Reprod. 2003;18(3):598–603.

41. Pache TD, Vladimiroff JW, Hop WC, Fauser BC. How to discriminate between normal and polycystic ovaries: transvaginal US study. Radiology. 2000;213(2):365–72.

42. Pau CT, Keefe CC, Welt CK. Cigarette smoking, nicotine levels and increased risk for metabolic syndrome in women with polycystic ovary syndrome. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2013;29(6):SS1–5.

43. Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M. Testosterone concentrations in women aged 25–50 years: associations with lifestyle, body composition, and ovarian status. Am J Epidemiol. 2001;153(3):256–64.

44. National Research Council (US) Committee on Passive Smoking. 1986. Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects [Internet]. Washington (DC): National Academies Press (US). Cited 2021 Jul 15. Available from: http://www.ncbi.nlm.nih.gov/books/NBK219205/