Menstrual cycle length and modern living: a review

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Purpose of review
The aim of this review is to evaluate biological, life history, environmental, and lifestyle factors and exposures that cause variability in menstrual cycle length (MCL).

Recent findings
Recent literature has detailed a number of factors that influence MCL, with particular emphasis placed on novel environmental exposures, such as air pollution and endocrine disrupting chemicals.

Summary
MCL varies widely in response to intrinsic and extrinsic inputs and is a useful predictor of reproductive health and fecundability.

Video abstract
http://links.lww.com/COE/A28

Keywords
endocrine disrupting chemicals, environmental exposures, fecundability, female reproductive health, menstrual cycle length

INTRODUCTION

Menstrual cycle length (MCL) is a relevant indicator of cycle regularity and reproductive health [1]. MCL is sensitive to inputs from the environment and varies within and between individuals [2], though a length between 24 and 38 days is considered normal [3]. Several factors cause MCL variability, including ovarian biomarkers [4] and lifestyle-based exposures [5]. Environmental exposures, such as air pollutants and endocrine disrupting chemicals (EDCs) pose a unique threat, as many are ubiquitous, persistent, and detrimental to reproductive health and MCL [6,7]. This review aims to discuss recent literature evaluating MCL variation in response to common and novel variables in modern life. We will also discuss MCL as an indicator or predictor of outcomes, such as endometriosis, polycystic ovary syndrome (PCOS), age at menopause, and fecundability.

METHODS

A literature search was conducted using PubMed to identify studies evaluating MCL and a number of biological, life history, environmental, and lifestyle exposures (shown as inputs in Fig. 1). Factors were identified using clinical and professional knowledge of prior literature. Novel exposures included air pollution and EDCs. Outputs (Fig. 1) were not included as search terms.

Search strategies are reported in Supplemental Table 1 (see Table, Supplemental Digital Content 2, http://links.lww.com/COE/A29, which lists queries used in the literature search). Searches used the terms 'menstrual cycle length' and 'cycle length' with one of the input variables in Fig. 1, using MeSH and non-MeSH terms. Search strategies excluded articles discussing MCL in populations with

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KEY POINTS

- A wide number of factors and exposures affect MCL, including novel environmental exposures, such as air pollution and EDCs, and lifestyle exposures, such as marijuana use.

- MCL is a valuable indicator of gynecological disorders like endometriosis and PCOS, as well as reproductive parameters, including age at menopause and fecundability.

- Research is needed to clarify inconsistent results regarding how MCL changes with certain exposures.

polycystic ovarian syndrome (PCOS). A limited number of relevant studies were published between 2020 and 2021, so inclusion criteria were expanded to include those with a publication date from 2016 to 2021. Most searches excluded studies not performed with human participants, though five necessitated the removal of this filter because of erroneous exclusion of relevant articles.

The searches yielded 268 results after duplicates were removed. Six additional articles were identified via citation searching and two were identified from knowledge of existing literature. Articles were excluded if they were not in English, were not primary studies, or were conducted in individuals with a reproductive disorder. Articles were excluded if they did not evaluate the association between MCL and variables included in the search strategies, or if they were not conducted using human participants. One article using a nonhuman primate model to study the effect

of marijuana use on MCL was included because of its relevance to the scope of the review and the lack of literature in humans. The screening process (Fig. 2) yielded a total of 38 relevant studies. The distribution of relevant studies by publication date is shown in Fig. 3.
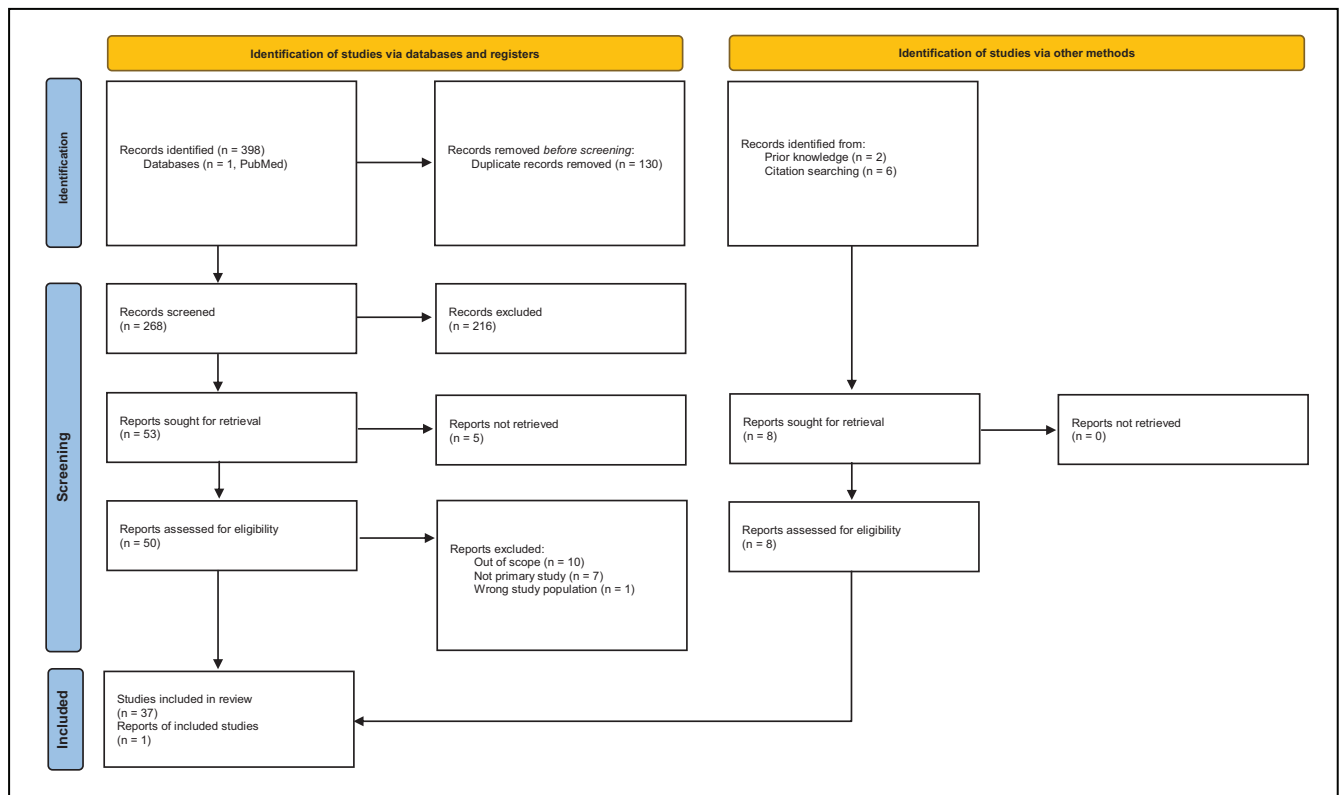
REVIEW

Intrinsic factors affecting MCL are presented first and include the following biological and life history factors of age, BMI and body weight, ovarian variables, genetics, age at menarche, and parity and breastfeeding. Extrinsic factors consist of the following environmental and lifestyle exposures: air pollution, EDCs, shift work, exercise, alcohol intake, smoking, and marijuana use.

Age

The way in which MCL and cycle length variability changes across the reproductive lifespan is well documented. Although most studies demonstrate a decrease in MCL during an individual's 30s and 40s [4,9,10,11■,12■], MCL increases as reproductive senescence approaches and shifts in an age-dependent manner [12■]. Follicular phase length also decreases with increasing age [9,11■], though results are inconsistent regarding whether luteal phase length changes appreciably. Others report that MCL variability changes with age. Notably, variation of 1.5–4.5 days is more common in individuals over 35 years [13■■] and mean MCL variation is highest (3.1 days) at age 45 years [9]. Previously reported
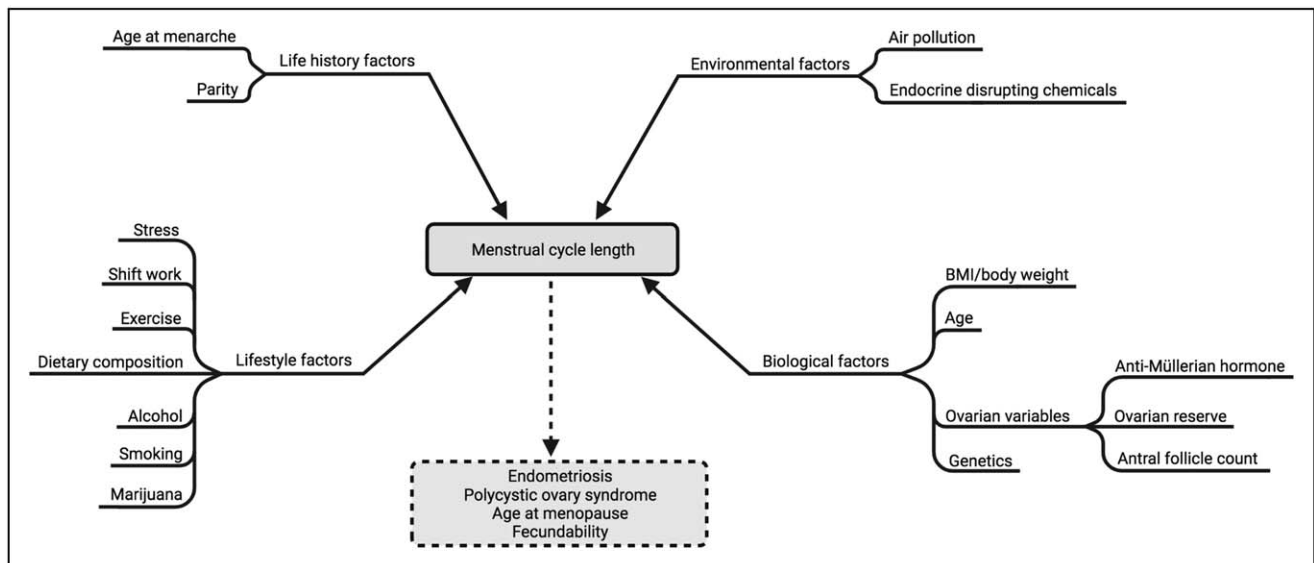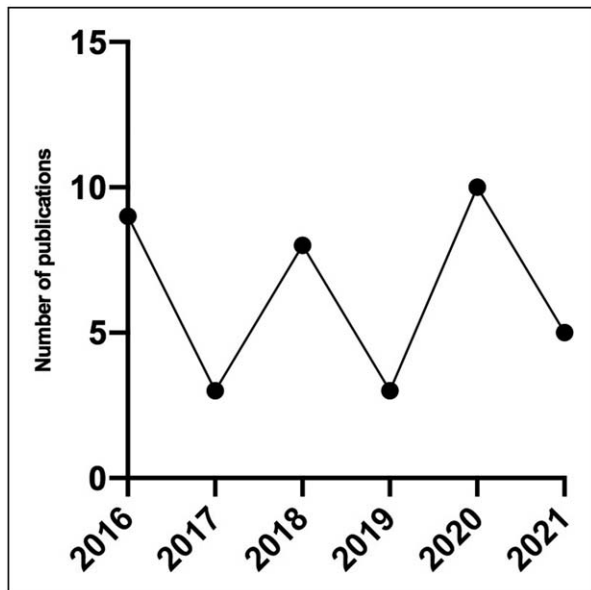

FIGURE 1. Menstrual cycle length inputs and outputs. Several biological, environmental, lifestyle, and life history inputs (solid lines) that are known to affect MCL were used as search terms. Output conditions (dotted lines), of which MCL was considered an indicator or predictor, were not included as search terms. Created with BioRender.com. MCL, menstrual cycle length.

FIGURE 2. PRISMA flow diagram describing the selection of articles included in this review. Data from [8]. For more information, visit http://www.prisma-statement.org/.

findings indicate that age-related decreases in MCL are because of earlier dominant follicle selection and folliculogenesis [14], whereas irregular cycles in older

FIGURE 3. Number of included articles published between 2016 and 2021. The number of relevant articles yielded by a PubMed literature search for associations between MCL and a number of variables and exposures from 2016 to 2021. MCL, menstrual cycle length.

individuals can be attributed to variability in the occurrence and timing of ovulation as they near the menopausal transition [2].

BMI and body weight

Grieger and Norman [13$^{\blacksquare\blacksquare}$] found that longer MCLs ($\geq$36 days) were more frequently associated with a BMI of 35–50 kg/m^2, though a large difference was only seen in individuals with a BMI greater than 50 kg/m^2. Though not all participants reported BMI, the proportion of overweight or obese individuals within the study population was similar to the general public. Others have found similar associations between higher body fat percentages (38.7–53.5%) and cycle lengths greater than 32 days [relative risk ratio (RRR) = 2.63; 95% confidence interval (CI) 1.21–5.69] [15$^{\blacksquare}$]. Over 70% of individuals experiencing longer MCLs had abdominal obesity in this study. Thus, the authors suggest that adipose tissue's endocrine functions play a role in modulating or altering hypothalamic–pituitary–ovarian signaling, leading to altered menstrual cycles [15$^{\blacksquare}$].

However, results on this topic are inconsistent. Bull *et al.* [9] found no association between BMI and MCL, though they were limited by the exclusion of nonovulatory cycles and a population not reflective of global obesity rates. Similar results were reported

in a prospective cross-sectional study of healthy women [mean BMI = 22.4 kg/m^2, standard deviation (SD) = 4] [4]. In other studies, a shorter mean MCL is associated with higher BMI [10]. Tayebi *et al.* [16] found a significant association between BMI and MCL ($P = 0.006$) in school-aged students (ages 9–18) but students with a BMI more than 30 were underrepresented in the sample. Inconsistent associations between BMI and MCL variability (the definition of which varies by study) have also been reported. Higher BMI is associated with increased MCL variability and irregularity (despite not being associated with short or long MCL) in two studies [9,17"] and decreased MCL variability in another [13""]. Roman Lay *et al.* [15"] propose that hormonal markers, such as sex hormone-binding globulin (SHBG), estrone (E1), and insulin may be partially mediating the interaction between measurements of weight and MCL. The underlying inconsistencies are likely because of cohort characteristics, study population, the assumption of ovulatory cycles for all episodes of bleeding, and varying definitions of MCL variability and irregularity.

Ovarian variables

Ovarian characteristics, such as anti-Müllerian hormone (AMH), ovarian volume, and antral follicle count (AFC) are associated with MCL. AMH, in particular, is the primary ovarian predictor of MCL and has a strong positive correlation with cycle length [4,18",19]. Zhu *et al.* [4] propose that AMH elongates follicular phase lengths by suppressing FSH-stimulated estradiol production from the antral follicles during folliculogenesis. A trend of increasing MCL was also seen with diminishing AMH, which is inversely correlated with increasing age [20]. Ovarian reserve and AFC are also both associated with AMH and MCL, though not to the same degree as AMH alone with MCL [4]. This association is likely because of the secretion of AMH by antral follicles and a proportional relationship between ovarian reserve and AMH.

Genetics

Three studies evaluate the genetic determinants of MCL. One reported that a polymorphism in the *FSHB* promoter (rs10835638; c.-211G>T) lowers follicle-stimulating hormone (FSH) levels and is associated with longer MCL [21]. As a threshold of FSH must be met for follicular recruitment, establishment of the dominant follicle, and ovulation to occur, the authors propose an association between the genetic determinants of FSH levels, ovulation, and parity, such that decreased FSH levels in individuals

with the polymorphism undergo ovulation less frequently, and therefore, have lower fecundability [21]. A genome-wide association study subsequently confirmed the association between the *FSHB* locus and MCL and highlighted four other loci of importance: *NR5A2, DOCK5/GNRH1, IGF2,* AND *PGR* [22]. These loci are involved in steroidogenesis, FSH/luteinizing hormone (LH) release, folliculogenesis, and progesterone signaling, respectively. Although a third study found the *FSHB* promoter polymorphism to be associated with significantly higher serum concentrations of FSH and LH, no significant association was found between the polymorphism and MCL [23]. However, the authors note their study was underpowered to assess this association.

Age at menarche

Whitcomb *et al.* [19] demonstrated that cycle lengths in individuals aged 18–22 years increased with later age at menarche. Conversely, data from a preconception cohort indicates that MCL is longer in individuals who reach menarche at a younger age [24]. Others have found no appreciable association between the two [4]. Conflicting results may be because of differences in study populations (Nurses' Health Study II [19] vs. preconception pregnancy planners [24] vs. healthy individuals recruited from a single site [4]), age at which MCL was evaluated (18–22 [19] vs. 21–45 years [4,24], and potential misclassification of MCL and age at menarche because of reliance upon patient self-report.

Parity and breastfeeding

Parity may be related to shorter MCL [11",24], though this association is sometimes weak [19] or nonexistent [4]. Additionally, breastfeeding appears to affect MCL. Najmabadi and colleagues [11"] report that individuals experienced shorter mean MCL (29.6 vs. 31.0 days), shorter follicular phases (18.5 vs. 19.1 days), and shorter luteal phases (11.0 vs. 11.7 days) when partially breastfeeding. Models used were stratified by age and parity but this study was limited by homogenous cohorts and lacked data regarding metabolic variables and lifestyle behaviors. Conversely, short MCL is associated with a shorter duration of breastfeeding in a model stratified by age [19].

Air pollution

Mahalingaiah *et al.* [7] found that individuals exposed to total suspended particulate in air have slightly increased odds of cycle irregularity and increased time to cycle regularity after menarche.

Furthermore, sulfur dioxide and particulate matter smaller than 10 µmol/l (PM$_{10}$) are associated with decreased luteal phase length [25]. In a separate study, levels of nitrogen dioxide (NO$_2$) and particulate matter smaller than 2. 5 µmol/l are associated with increased follicular phase length, though neither NO$_2$ nor PM$_{10}$ are associated with increased luteal phase length [26▪]. These results indicate that exposure to particulates released by fuel combustion may alter HPO signaling via endocrine disruption, thereby affecting MCL, possibly through lengthened follicular phases or luteal phase deficiency [6].

Endocrine disrupting chemicals

Studies have reported concerning associations between EDC exposure and MCL. Notably, many are limited by small sample size. Three prospective cohort studies reported variability in MCL following exposure to perfluoroalkyl substances (PFAS) [10,27,28]. Though Singer *et al.* [27] found no association between PFAS concentrations and MCL, subgroup analyses linked decreased perfluoroheptane sulfonate and perfluorooctane sulfonate (PFOS) levels to short MCL in parous individuals, and increased perfluorononanoic acid (PFNA) and perfluoroundecanoic acid levels to long MCL in individuals who had used oral contraceptives in the previous year. Interestingly, higher perfluorooctanoic acid (PFOA) concentrations are associated with decreased MCL in one study [10] but increased levels of PFOA, PFNA, perfluorohexane sulfonate, and PFOS are associated with MCL more than 35 days in another [28].

The impact of organohalogen exposure on MCL has likewise been of interest. A prospective cohort study showed no significant association between prenatal exposure to persistent organochlorine pollutants or polychlorinated biphenyls and MCL but did find that other aspects of reproductive health were impacted [29]. Recently, a study demonstrated that long and irregular cycles were common in Latinx child and adolescent farmworkers exposed to pesticides, including pyrethroids, organochlorines, and organophosphates [30▪]. The study detected pesticide exposure using wristbands but the results are limited as wristbands were worn for 1 day. Conversely, increasing concentrations of persistent organohalogens and elements, particularly polybrominated diphenyl ethers, cadmium, and selenium, are associated with decreasing MCL, whereas increased MCL is associated with higher concentrations of copper [31].

Remaining studies evaluate MCL following exposure to several other EDCs. A prospective cohort study reported increasing average MCL with increased exposure to polybrominated biphenyls (PBBs), though this was not statistically significant [32]. Moreover, a study linked shorter MCL and higher urinary concentrations of parabens, which are used as preservatives in personal care products and demonstrate estrogenic activity [33]. A similar association was reported between shorter luteal phases and higher urinary concentrations of phthalates and bisphenol A in a prospective cohort study, though no associations were found with follicular phase length [34]. Conversely, in a cross-sectional study assessing exposure to n-hexane, a volatile organic compound, 79% of exposed individuals demonstrated MCL more than 35 days vs. 20% in the control group ($P = 0.007$) [35▪]. Finally, a prospective cohort study evaluated the effect of dietary phytoestrogens and found that, though phytoestrogens were not associated with MCL, they may be associated with cycle regularity [36].

Stress

Whether a relationship exists between stress and MCL remains unclear, likely in part because studies rely on self-reports of perceived stress levels. Of note, physical stress from exercise or caloric restriction is not included in this conceptualization of stress. Nonetheless, among those that are still menstruating and not affected by stress-induced hypothalamic amenorrhea, increased perceived stress (noted on a questionnaire) is associated with shorter MCL [13▪▪] and increased MCL irregularity [37]. The latter result is supported by Phelan *et al.* [38▪], who assessed how stress associated with the COVID-19 pandemic impacted menstrual characteristics. Cycle length, however, was not found to change significantly before and during the pandemic [38▪], and a separate study similarly reported no significant relationship between MCL and perceived stress [4].

Shift work

Although one study found no significant association between average hours of sleep, shift work, and MCL [4], others indicate that MCL is impacted by disrupted circadian rhythm [5,39,40▪]. The frequency of night shifts is associated with shortened MCL and shift work schedules are associated with increased likelihood of cycle irregularity in a study containing both cross-sectional and nested case–control components [39]. Particularly concerning is that these changes had not recovered 2 years later [39]. Another cross-sectional study similarly found that rotating shifts were associated with MCL irregularity [40▪]. Sleeping for fewer than 6 h per night is also significantly associated with short MCL (OR = 3.7; 95% CI 1.1–12.7) and nonsignificantly associated with long

MCL (OR = 1.7, 95% CI 0.8–3.7) in a prospective cross-sectional study, leading the authors to suggest a causal association between insufficient sleep and metabolic abnormalities [5].

Exercise

Three studies evaluated MCL and exercise frequency but did not differentiate between types of exercise. Of these, two found that exercise frequency did not significantly change MCL [4,5]. The third showed that individuals with short cycles were more likely to report no regular exercise than those with normal or long MCL [13""]. One prospective cohort study utilized the frequency of different exercise types to assess metabolic expenditure, concluding that individuals with shorter cycles had higher metabolic equivalent task-hours per week than individuals with MCLs between 26 and 31 days [19].

Dietary composition

Two studies evaluated the influence of diet on MCL within the review period. A cross-sectional study found that individuals with a low adherence to a Mediterranean diet had longer MCL than those whose regular diet more closely resembled a Mediterranean diet ($P < 0.01$) [41"]. A second study reported moderate differences in MCL associated with dietary factors, including dietary percentage of vegetable protein, vitamin D, energy, and dairy [19].

Alcohol

Most studies show no association [4,13""] or a weak association [19] between MCL and alcohol consumption. One cross-sectional study found a positive correlation between the daily quantity of alcohol consumed and MCL in individuals aged 18–35 ($r = 0.119$, $P = 0.038$) [41"]. Inconsistencies in results may be because of differences in how alcohol intake is assessed (e.g. intake frequency [4,13""] vs. quantity consumed per day [19,41"]), sample recruitment (e.g. single site [4,41"] vs. national [19] vs. global [13""]), reliance upon self-report for MCL and alcohol consumption, and whether participants using oral contraceptives were included [41"] or not [4,13"",19].

Smoking

Two recent studies found no association between MCL and smoking status measured by active smoking (yes/no) [4] and smoking regularity (regularly/sometimes/do not smoke) [13""]. Conversely, three studies report that smoking, including pack-years [19], and active smoking status [10,17"], was associated with shorter MCL (<25 days). Again, variation in how smoking status was assessed (smoking regularity [13""], number of cigarettes per day [17",19], active smoking [4], and blood concentration of nicotine biomarkers [10]) may explain the contrasting results.

Marijuana

One study evaluated how marijuana use affects MCL in humans, and a second study using a nonhuman primate model was identified through outside knowledge. A randomized controlled trial found individuals co-using marijuana and tobacco experience a significantly shorter luteal phase [11.4 days ± 2.2 (SD)] than participants who only use tobacco [16.8 days ± 11.3 (SD); $P = 0.002$] [42]. However, the authors reported no differences in follicular phase length or overall MCL, and conclusions were limited by lack of information regarding the frequency and quantity of marijuana used and combined use of tobacco and marijuana. Conversely, average MCL increased in a dose-dependent manner (4 days for each mg/7 kg/day of tetrahydrocannabinol (THC)) (95% CI 1.4–6.6 days; $P = .002$) in rhesus macaques given chronic, heavy doses of THC edibles [43"]. Though only one blood sample was taken at each dose increase, the frequency and quantity of THC ingested were closely controlled.

DISCUSSION

These studies are evidence of the extent to which MCL is sensitive to internal biological factors and external exposures. The purpose of this review is to provide an update to factors, which have been the subject of publications in recent years, including novel exposures, such as air pollution and EDCs. Literature published prior to the review period has documented MCL varying in response to factors not discussed here, such as caffeine intake [44], oral contraceptive use and cessation [45], miscarriages [45], and race and ethnicity [46]. Studies identified within this review serve to further document the response of MCL to everyday life. Of particular importance are those which evaluate the association between MCL and novel environmental and lifestyle exposures. It is likely that, as individuals experience increased cumulative exposures to air pollution and EDCs and increased availability and accessibility of marijuana, MCL disturbances may become more common.

Furthermore, MCL serves as an indicator of general and reproductive health. MCL has previously been associated with differences in reported

menstrual cycle symptom patterns [47], postmenopausal fracture risk [48], and mental illness [49]. In the context of reproductive health, MCL is an indicator of cumulative hormone exposure [50] and a predictor of age at menopause [19]. Indeed, individuals who experience cycle lengths less than 25 days at ages 18–22 years are at a higher risk of early menopause, suggesting accelerated oocyte depletion as the cause [19]. MCL can also be assessed as both a risk factor and a symptom of gynecologic disease. For example, short MCL increases an individual's risk for endometriosis because of more frequent exposure to retrograde menstruation [51]. MCL is also associated with PCOS, such that longer MCLs are considered a symptom of the disorder [52] and the ovarian variables that are significantly associated with MCL are strongly linked to the pathophysiology of PCOS [4].

One of the most impactful applications of the presented information pertains to fecundability. Intervals of 27–29 [24], 30–31 [53], and 32–33 days [54] have the highest fecundability among MCLs within the normal range within a population of women of childbearing age or those attempting conception. Moreover, MCL is strongly correlated with successful in-vitro fertilization treatments [55]. These findings highlight the value of using MCL as a predictor of fecundability in a clinical context.

Notably, there are cautions to be taken when assessing studies on MCL, many of which rely on self-reporting to determine menstrual characteristics. Moreover, comparing data between studies is complicated by inconsistent definitions of normal, short, or long MCLs (e.g. long MCL being ≥32 days [15▪] vs. >45 days [30▪]) and MCL variability. Researchers have previously proposed that some factors affect MCL more dramatically in individuals predisposed to shorter or longer cycles, therefore, complicating the ability to draw broad conclusions about how a given factor affects an entire population [56].

CONCLUSION

This review demonstrates how MCL varies in response to a number of biological, life history, environmental, and lifestyle factors in a way that impacts reproductive health. With the rise in cycle tracking apps, it is likely that population-level data will become available as large datasets that are used to obtain broader MCL patterns. Further research will elucidate the physiological mechanisms underlying these changes and further our understanding of topics that are new (like the genetic determinants of MCL) or underrepresented in research (like the effect of marijuana on reproductive health).

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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