Abstract

Objectives: To examine the prospective association between menstrual symptoms before pregnancy and preterm birth.

Methods: Secondary analysis of data from 14,247 young Australian women born between 1973 and 1978 who participated in a longitudinal, population-based cohort study between 1996 and 2015. Women were first surveyed at 18-23 years and seven waves of data were collected at roughly three-yearly intervals. At each survey, women were asked about 'severe period pain', 'heavy periods' and 'irregular periods' within the last 12 months. From 2009 onwards, information on their children was collected, including birth dates and preterm birth (<37 weeks). Logistic regression using generalised estimating equations was used to examine prospective associations between self-reported menstrual symptoms before pregnancy and risk of preterm birth.

Results: Data from 6,615 mothers, who had 12,337 live singleton births were available for analysis. Among all births, women reporting severe period pain [adjusted odds ratio (aOR) 1.34, 95% CI 1.10–1.62] or heavy periods (aOR 1.25, 95% CI 1.02–1.53) before pregnancy had higher odds of preterm birth. However, in analyses stratified by birth order, only severe period pain (aOR 2.05, 95% CI 1.41–2.99), heavy periods (aOR 1.77, 95% CI 1.23–2.55) or irregular periods (aOR 1.58, 95% CI 1.10–2.28) prior to a second or subsequent birth were associated with an increased risk of preterm birth.

Conclusions: Severe period pain, heavy periods and irregular periods before a second or subsequent birth may be associated with preterm birth.

Keywords preterm birth, dysmenorrhea, heavy menstrual bleeding, irregular periods, cohort study

Background

Preterm birth, defined as birth prior to 37 weeks, occurs in 5-10% of all pregnancies and the prevalence has increased in high-resource countries [1-3]. Preterm birth is a major cause of neonatal mortality and child morbidity, including neurological, respiratory and cardiovascular disorders [4]. Preventative strategies are challenging because there is uncertainty about the underlying causes of preterm birth[5]. For approximately half of mothers, there will be no identifiable cause for these conditions [1,5,6]. However, commonly reported maternal risk factors for preterm birth include very young and advanced maternal age, infections, medical conditions before and during pregnancy (e.g., hypertension, diabetes), and smoking [1,6,7].

Hormonal and inflammatory influences before and during pregnancy also play important roles in adverse pregnancy and neonatal outcomes[8]. Menstrual cycle characteristics, including dysmenorrhea and irregular periods, can be important indicators of hormonal imbalances, inflammation and of a woman's risk of future health problems [9,10]. Approximately one quarter of women report dysmenorrhea, [11] and a third report irregular periods [9]. Although menstrual symptoms can decrease across the life course, some women will experience chronic symptoms throughout their reproductive years [11]. Risk factors for chronic dysmenorrhea include smoking and obesity [11], which are also risk factors for adverse pregnancy outcomes [12].

Studies examining how menstrual symptoms influence birth outcomes are scant. Two small, case-control studies from Finland and Taiwan reported an association between dysmenorrhea and preterm birth [13,14]. However, the study from Finland was conducted more than three decades ago, relied on women's retrospective reports of menstrual symptoms, and did not consider other risk factors. The more recent study from Taiwan used medical records to

confirm women's birth outcomes, but dysmenorrhea was also collected retrospectively at the first prenatal visit. Data from larger, more comprehensive studies, that can examine prospective associations are important for identifying pre-pregnancy risk factors that can inform timely preventative interventions for preterm birth.

In this paper, we use data from 12,337 singleton births from 6,615 women who participated in a longitudinal, population-based cohort study to examine the prospective associations between menstrual symptoms; we also account for the mother's physical, mental and reproductive health history.

Methods

The Australian Longitudinal Study on Women's Health (ALSWH) is a national study focusing on the biological, psychological, social and economic factors relevant to women's health [15]. The women were randomly selected from the database of Medicare (Australia's universal health insurance system), with oversampling from rural and remote areas of Australia. Approximately every three years since 1996, participants have completed postal or online surveys about their health and wellbeing [15,16]. Detailed information on the study methods has been published elsewhere [16,17] and is available at http://www.alswh.org.au/.

Participants

A total of 14,247 young women participated in the baseline survey in 1996 when they were aged 18-23 years. Of these, 8,349 women had 18,525 live births between 1996 and 2015 (see Figure 1). Overall, we excluded 6,188 (33%) births and 1,734 (21%) mothers due to births that occurred before the baseline survey in 1996 (1,102 births from 170 mothers); multiple births (628 births from 95 mothers) and births from mothers who had missing data for

menstrual symptoms (2,184 births), the first birth (1,193 births from 743 mothers) or preterm birth (1,081 births from 726 mothers). A final sample of 12,337 live singleton births from 6,615 mothers were available for analysis (see Figure 1). Of these, 4,454 (67.3%) mothers had two or more singleton births by Survey 7 when they were aged 37-42 years.

Measures

Women were asked about their birth history at Survey 5 (2009), Survey 6 (2012), and Survey 7 (2015). For each birth, participants were asked to report the date of birth for each child and if they had experienced: "Premature birth". Using each infant's date of birth and the date when the mother returned each survey, births were matched to the mother's survey before the birth. This information was also used to ascertain maternal age at birth (calculated using the mother's date of birth at the time of the child's date of birth), birth order (first birth vs. subsequent birth) and history of preterm birth (dichotomised as yes vs. no).

Women were also asked about their reproductive health including menstrual symptoms. At each survey, three separate questions were asked: "In the last 12 months, have you had: 1) severe period pain; 2) heavy periods; 3) irregular periods?". Separate variables were created for each question; those who answered "sometimes" or "often" were coded as having that symptom, and those who responded "never" or "rarely" were coded as not having the symptom. Other aspects of reproductive health including a history of miscarriage, doctor diagnosis of polycystic ovary syndrome (data collected from Survey 4 onwards) and endometriosis (all dichotomised as yes vs no) were also collected.

Sociodemographic information was also collected at each survey including area of residence based on an index of distance to the nearest urban centre (urban vs. rural/remote) [18]; highest

level of education (year 12 or less, trade/certificate/diploma, university degree) and current relationship status (single, married/defacto partnership). Women were also asked about smoking (classified as never, ex-smoker, current smoker) and body mass index [(BMI;kg/m^2) calculated using women's self-reported weight and height, and categorised as underweight (<18.5kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight or obese (≥25 kg/m^2). Information was collected on chronic health conditions prior to pregnancy including hypertension or diabetes (dichotomised as yes vs. no), general mental health (using the 5-item Mental Health subscale (MHI-5) of the SF-36) [19].

Statistical analyses

Chi-square tests and independent samples t-tests were used to compare the characteristics of nulliparous women, up to three years prior to their first birth, who subsequently did, or did not experience preterm birth. Using each mother's longitudinal birth outcome data, logistic regression models using generalised estimating equations with exchangeable working correlation matrices and robust error variances, were used to account for repeated births nested within mothers. Separate models assessed the association between each menstrual symptom and preterm birth.

All covariates were those reported by the woman at the survey before the index birth, except maternal age, which was based on the participant's age at the time of the birth. All covariates were initially included in the models together to assess associations with birth outcomes. Area of residence, education, smoking, mental health, miscarriage, polycystic ovary syndrome and endometriosis were not statistically significant ($p > 0.05$) or did not change odds ratio estimates by more than 10%, and thus, were not included in the final models. Final models were adjusted for maternal age at birth, BMI, hypertension or diabetes (combined into

one variable for the analysis), birth order and previous preterm birth. To account for the possibility that women's menstrual symptoms changed between births, an interaction term between each menstrual symptom and birth order (first birth vs. subsequent birth) was included in the models and further analyses stratifying by birth order were completed.

There were moderate levels of missing data on the key maternal exposures (severe period pain = 12.1%; heavy periods = 12.2%; irregular periods = 12.2%) and covariates (hypertension = 14.8%; diabetes = 14.8%; BMI = 20.5%). The influence of missing data on the exposures and covariates on the results was assessed in a multiple imputation analysis [20]. The variables used in the imputation procedure included the outcome variable, exposures (menstrual symptoms) and covariates (maternal age, education, area of residence, marital status, parity, age at menarche, smoking, BMI, hypertension, diabetes). The following SAS procedures were performed: PROC MI using fully conditional specification (due to the binary nature of the key exposures and outcomes) was used to create 20 imputed datasets; logistic regression analyses using generalised estimating equations were performed on each of the imputed datasets; and results were combined using MIANALYZE. Findings based on original data are presented, as these did not differ from findings based on the imputed data. All statistical analyses were performed using SAS software version 9.4 (TS1M5) [21].

Results

A total of 12,337 live singleton neonates born between 1996 and 2015 were eligible for analysis. Of these births, 6.3% (n = 779) were preterm. The percentage of preterm births was 8.5% (564/6,615) in a first birth and 3.8% (215/5722) in a second or subsequent birth. Table 1 shows the characteristics of the 6,615 women who gave birth to the 12,337 children between 1996 and 2015. Women who went on to have a preterm birth were more likely to be younger, residing in a rural or remote area, married and to have completed 12 years or less

148 years of education at the survey prior to their first birth than women who did not have a
149 preterm birth (see Table 1). They were more likely to be overweight or obese, current
150 smokers, and to report a diagnosis of hypertension or diabetes. Women who went on to have
151 a preterm birth were more likely to have a history of miscarriage, a diagnosis of polycystic
152 ovary syndrome or endometriosis and poorer mental health prior to their first birth than
153 women who did not have a preterm birth (see Table 1).
154
155 Menstrual symptoms before pregnancy among women who did, or did not, have a preterm
156 birth are presented in Table 2. Before a first birth, severe period pain did not appear to differ
157 among women who did, and did not, have a preterm birth. Specifically, 30.0% of nulliparous
158 women who went on to have preterm birth reported severe period pain. By comparison,
159 26.3% of nulliparous women who did not have a preterm birth reported severe period pain.
160 However, menstrual symptoms differed among women who did, and did not, have a
161 subsequent preterm birth. For subsequent births, 24.9% of women who had a preterm birth
162 reported severe period pain compared to 13.4% who did not have a preterm birth ($p < 0.001$).
163 This pattern was similar for the other menstrual symptoms. Specifically, heavy periods and
164 irregular periods before pregnancy did not differ among women whose first birth was, or was
165 not, preterm. For subsequent births, 25.6% of women who had a preterm birth reported heavy
166 periods compared to 16.1% among women who did not have a preterm birth ($p < 0.001$).
167 Similarly, 25.8% of women who had a subsequent preterm birth reported irregular periods
168 compared to 16.6% who did not have a subsequent preterm birth ($p < 0.001$).
169 Longitudinal multivariable models were constructed to examine the associations between
170 each menstrual symptom and preterm birth. For all births, severe period pain before
171 pregnancy was associated with higher odds of preterm birth (OR 1.58, 95% CI 1.33–1.88),
172 and this association remained after adjustment for other key covariates [adjusted OR (aOR)

1.33, 95% CI 1.10–1.62] (Table 3). However, there was a significant interaction between birth order and severe period pain (*p* for interaction = 0.01) suggesting that birth order modified the association between severe period pain and preterm birth. In analyses stratified by birth order, severe period pain before a first birth was not associated with preterm birth. Only women reporting severe period pain before a second or subsequent birth had higher odds of preterm birth (aOR 2.05, 95% CI 1.41–2.99). These results were similar for heavy periods with an increased risk of preterm birth among all births (aOR 1.24, 1.01–1.53) and for women reporting heavy periods before a second or subsequent birth (aOR 1.78, 1.24–2.56). Although there was no overall association between irregular periods and preterm birth, there was a significant interaction between birth order and irregular periods (*p* for interaction = 0.01). In analyses stratified by birth order, only women reporting irregular periods prior to a second or subsequent birth had higher odds of preterm birth (aOR 1.59, 1.10–2.29).

Discussion

Using a large, population-based cohort study we examined the associations between menstrual symptoms and preterm birth. In this study, the strongest associations between menstrual symptoms and preterm birth were found after a first birth. Specifically, the chances of preterm birth were greater among women reporting severe period pain, heavy periods and irregular periods before a second or greater birth.

Underlying maternal medical conditions may play an important role in explaining our findings. Although there is evidence to suggest that dysmenorrhea is less likely after birth [22], any benefits attributable to a recent birth may be short term for women who have underlying conditions. Such underlying conditions may damage the uterine environment, manifesting as menstrual problems and increased risk of poor subsequent birth outcomes. Endometriosis is a

common cause of severe period pain, heavy periods, and irregular periods [10,22], and has been previously associated with preterm birth[23]. A recent systematic review found limited evidence to suggest that symptoms of endometriosis improve following pregnancy [24]. The persistence of menstrual problems beyond a first birth may therefore identify women who have more severe symptoms and may be a marker for underlying conditions and future health problems. During pregnancy, the hormonal and inflammatory changes associated with endometriosis may negatively affect the uterine environment [25], or contribute to complications in pregnancy (e.g., placenta praevia) [26], increasing the chances of preterm birth. Because considerable delays in diagnosis are common for women who have endometriosis[27], some women with severe period pain and heavy menstrual bleeding in our study may have had undiagnosed disease. As the disease progresses over time, this may lead to further scarring and adhesions that increase the risk of problems in subsequent pregnancies. However, adjusting for a history of endometriosis did not change the association between menstrual symptoms and preterm birth in this study.

Menstrual problems may also be an indicator of other underlying hormonal, endocrine, or metabolic conditions that increase the risk of pregnancy complications. In this study, heavy periods or irregular periods before a second or greater pregnancy increased the odds of preterm birth. Heavy and irregular periods are a common feature of polycystic ovary syndrome[28], which is also related to a range of adverse pregnancy outcomes including preterm birth [29,30]. However, in this study, adjusting for polycystic ovary syndrome did not appreciably change our findings. Alternatively, heavy periods have been associated with problems in the production of progesterone [31]. Because progesterone plays a key role in the maintenance of pregnancy, insufficient levels of progesterone in women may increase the risk of preterm birth[32]. Clinically, progesterone is used to prevent preterm birth in women

222 who have premature cervical shortening in pregnancy, however, the efficacy of the treatment
223 has been contentious [33-35]. Chronic conditions associated with increasing age (e.g., obesity,
224 diabetes) can also disrupt the production of progesterone and lead to heavy periods [31];
225 however, these conditions and maternal age were taken into account in our analyses. Other
226 gynaecological conditions (e.g., uterine fibroids, adenomyosis) [31], which were not assessed in
227 this study, might help to explain the association between menstrual problems and preterm
228 birth.

229

230 Interventions during a first birth may further help to explain our findings. Recent evidence
231 suggests that having had a caesarean birth is a risk factor for preterm birth among
232 multiparous women [36]. In Australia, caesarean birth rates are high (33% of all births in 2015)
233 and have increased over time [37]. In another study also based on data from the young women
234 participating in ALSWH, 29% of first, singleton births were caesarean births, which is
235 consistent with national estimates [38]. The risks of caesarean birth are well-established and
236 increase with each subsequent caesarean birth [39]. Adhesions, surgical injury or infections
237 following a caesarean birth [40] may change women's menstrual symptoms following a first
238 birth. Uterine changes associated with caesarean birth may help to explain the increased odds
239 of preterm birth in second and greater births in this study.

240

241 There may also be complex interactions between hormonal, metabolic, and inflammatory
242 pathways that influence a woman's uterine environment after a first pregnancy, and
243 negatively affect their future pregnancy outcomes [8]. The composition of the vaginal
244 microbiome may help to explain how hormonal and inflammatory pathways interact to
245 influence menstrual symptoms and the risk of preterm birth, particularly in subsequent

246 pregnancies. Bacterial vaginosis[41], and more recently certain species in the vaginal
247 microbiome[42,43], have been linked to preterm birth. There is evidence to suggest that the
248 composition of the vaginal microbiome changes during pregnancy and differs from the
249 composition in the postpartum period, which may be due to the significant hormonal changes
250 during these periods[44]. Menstrual symptoms are often important markers for hormonal
251 imbalances in women[8] and may also be linked to changes in the vaginal microbiome.

252

253 Hypothetically, imbalances in vaginal microbiota following a first birth may give rise to
254 inflammatory processes[42] and present as menstrual problems, thereby increasing adverse
255 outcomes in subsequent pregnancies. During pregnancy, the up-regulation of pro-
256 inflammatory responses among women with an abundance of certain bacterial species may
257 trigger the release of prostaglandins, or erode mucosal barriers that normally protect women
258 from infection, and increase the risk of premature labour[45]. If vaginal microbiota were an
259 underlying mechanism, women presenting with a history of menstrual problems following a
260 first birth might benefit from treatments that modify the vaginal microbiome in their next
261 pregnancy. Although oral probiotic supplements to modify the vaginal microbiome are
262 potentially a low-risk intervention that can be leveraged to reduce preterm birth rates, their
263 effectiveness has yet to be demonstrated[46]. The associations observed in this study, and the
264 role of the vaginal microbiome in preterm birth, warrants further investigation.

265 The main advantage of this longitudinal, population-based cohort study is that prospective
266 relationships between menstrual symptoms and subsequent preterm birth were examined. We
267 were also able to assess the contribution of an extensive range of covariates including
268 sociodemographic factors, and physical, psychological and reproductive health. Although
269 some women were lost to follow-up or withdrew over the 20-year study period, continued
270 participation has remained relatively stable at more than 80% [47]. Women who remain in this

study are broadly representative of the general population of Australian women in this age group with a few exceptions. A slightly higher proportion of women who remain in the study are married or in de facto relationships and have university degrees [16,17].

This study has some important limitations. All information was based on self-report questionnaires rather than hospital records, which may mean that preterm birth, menstrual symptoms and other covariates assessed in this study were over- or under-reported. Another study comparing self-reported perinatal outcomes in ALSWH to hospital records demonstrated high agreement between the two sources [48]. However, because ALSWH is a broad-ranging health study not specific to birth outcomes, information was not available to distinguish between early and late preterm births or to determine whether the preterm birth was spontaneous or medically indicated. The timing of the ALSWH surveys also means that information on women's menstrual symptoms and the other key covariates may have occurred three years prior to the index birth. In addition, infants born to women who had two or more pregnancies between successive surveys were excluded as menstrual symptom data before that birth were missing. Therefore, we are unable to establish whether a causal association exists between menstrual symptoms and preterm birth.

Overall, our findings suggest that menstrual problems that continue or emerge after a first birth are risk factors for preterm birth. These findings emphasise the potential clinical importance of reviewing women's menstrual symptoms in early pregnancy, especially among women in a second or subsequent pregnancy. In Australia, there have been recent efforts to reduce preterm births rates through increased health provider education and the implementation of evidenced-based recommendations[49]. These recommendations reinforce the need to measure cervical length at all mid-pregnancy morphology scans and to provide

296 vaginal progesterone pessaries for women at risk based on their cervical length or maternal
297 history[49]. Currently, Australian health providers should counsel women based on these
298 recommendations. In the future, women's menstrual symptom history could be used in
299 conjunction with other aspects of maternal medical history to better identify women at risk of
300 preterm birth. However, future research is required to confirm the association between
301 menstrual symptoms and women's birth outcomes.
302

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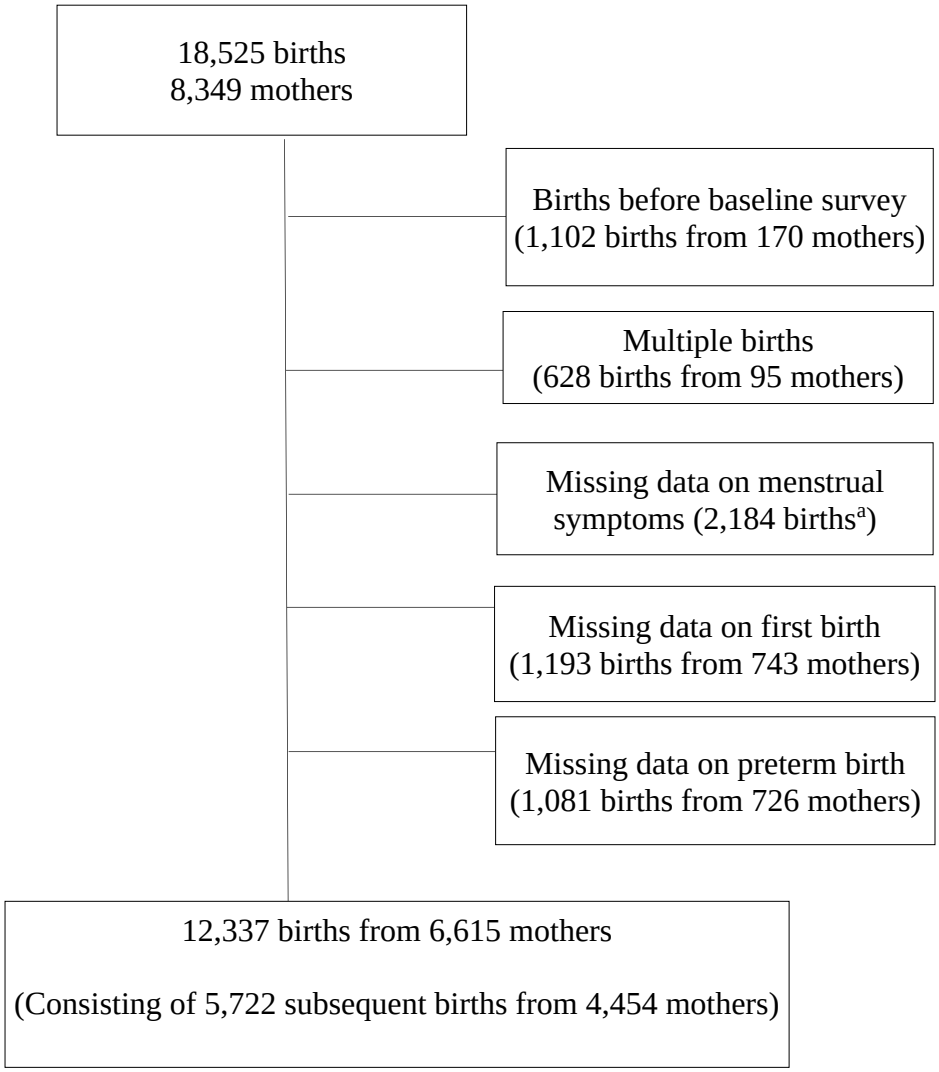

[a]Data from births were only missing because the mother had one record of menstrual symptoms but two births between surveys.

463 **Figure legends**

464 Figure 1. Flow diagram of the births between 1996 and 2015 from Australian mothers who

465 met the inclusion criteria.

466 Table 1. Characteristics of Australian women prior to the first birth who subsequently did, or
467 did not, have a preterm birth between 1996-2015. N = 6615

	No Preterm birth *n* = 5887	Preterm birth *n* = 728
	n (%)	*n* (%)
Age (years)***		
18-24	1179 (22.9)	168 (26.9)
25-29	2170 (42.2)	289 (46.3)
30-34	1438 (28.0)	134 (21.5)
35-40	356 (6.9)	33 (5.3)
Area of residence*		
Urban	2926 (57.8)	330 (53.6)
Rural/Remote	2133 (42.2)	286 (46.4)
Marital status**		
Single	973 (19.0)	148 (23.8)
Married/De facto	4157 (81.0)	473 (76.2)
Education**		
Year 12 or less	1343 (26.5)	193 (31.3)
Trade/certificate/diploma	1213 (23.9)	154 (25.0)
University	2516 (49.6)	269 (43.7)
Body mass index**		
Underweight	194 (4.3)	29 (5.2)

	No Preterm birth *n* = 5887	Preterm birth *n* = 728
	n (%)	*n* (%)
Healthy weight	2900 (64.2)	316 (56.8)
Overweight	950 (21.0)	135 (24.3)
Obese	472 (10.5)	76 (13.7)
Smoking**		
Never smoked	3069 (60.3)	342 (54.9)
Ex-smoker	1109 (21.8)	139 (22.3)
Current smoker	914 (17.9)	142 (22.8)
Diabetes[a**]		
No	4961 (99.4)	599 (98.4)
Yes	31 (0.6)	10 (1.6)
Hypertension[a***]		
No	4870 (97.6)	561 (92.1)
Yes	121 (2.4)	48 (7.9)
Miscarriage**		
No	4588 (90.1)	535 (86.7)
Yes	503 (9.9)	82 (13.3)
Polycystic ovary syndrome***		
No	5352 (92.6)	621 (87.8)

	No Preterm birth	Preterm birth
	n = 5887	*n* = 728
	n (%)	*n* (%)
Yes	429 (7.4)	86 (12.2)
Endometriosis**		
No	4673 (95.8)	557 (93.6)
Yes	203 (4.2)	38 (6.4)
Mental health score (MHI-5)***	Mean ±SD	Mean ±SD
	73.1 ±16.1	70.2 ±16.7

Note. Data were reported up to three years prior to the first birth.

[a]Prior to pregnancy

SD, standard deviation.

*P = <.05; **P = <.01; ***P = <.001

472 Table 2. Menstrual symptoms before pregnancy among Australian women who subsequently
473 did, or did not, have a preterm birth between 1996-2015, by birth order. N = 6615

	No Preterm birth	Preterm birth
	n (%)	*n* (%)
Severe period pain before first birth		
No	3867 (73.7)	340 (70.0)
Yes	1382 (26.3)	146 (30.0)
Severe period pain before subsequent birth***		
No	4268 (86.6)	133 (75.1)
Yes	659 (13.4)	44 (24.9)
Heavy periods before first birth		
No	4271 (81.5)	385 (79.2)
Yes	972 (18.5)	101 (20.8)
Heavy periods before subsequent birth***		
No	4131 (83.9)	131 (74.4)
Yes	794 (16.1)	45 (25.6)
Irregular periods before first birth		
No	4198 (80.0)	391 (80.5)
Yes	1049 (20.0)	95 (19.6)
Irregular periods before subsequent birth***		
No	4107 (83.4)	132 (74.2)

	No Preterm birth	Preterm birth
	n (%)	*n* (%)
Yes	819 (16.6)	46 (25.8)

Note. Data were reported up to three years prior to the birth.

Subsequent birth = Refers to a second or greater birth.

*P = <.05; **P = <.01; ***P = <.001

Table 3. Association between menstrual symptoms reported by Australian women and preterm birth between 1996-2015. N = 12,337

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Severe period pain (all births)	1.58 (1.33–1.88)	1.34 (1.10–1.62)[a]
Stratified by birth order		
First birth	1.20 (0.98–1.47)	1.18 (0.95–1.48)[b]
Subsequent birth	2.01 (1.40–2.88)	2.05 (1.41–2.99)[c]
Heavy periods (all births)	1.34 (1.11–1.61)	1.25 (1.02–1.53)[a]
Stratified by birth order		
First birth	1.15 (0.92–1.45)	1.08 (0.84–1.39)[b]
Subsequent birth	1.65 (1.16–2.35)	1.77 (1.23–2.55)[c]
Irregular periods (all births)	1.17 (0.96–1.41)	1.05 (0.85–1.30)[a]
Stratified by birth order		
First birth	0.97 (0.77–1.23)	0.89 (0.69–1.15)[b]
Subsequent birth	1.67 (1.19–2.33)	1.58 (1.10–2.28)[c]

Note. Menstrual symptoms refer to those preceding the index pregnancy (up to 3 years before birth). Subsequent births are second or greater births.

[a]Adjusted for maternal age, BMI, hypertension/diabetes, parity and previous preterm birth

[b]Adjusted for maternal age, BMI, hypertension/diabetes

[c]Adjusted for maternal age, BMI, hypertension/diabetes and previous preterm birth