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BIRTH WEIGHT AND CHILDHOOD GROWTH IN DAUGHTERS OF WOMEN WITH IRREGULAR MENSTRUAL CYCLES

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Abstract

Menstrual irregularity has been associated with insulin resistance, type 2 diabetes mellitus, and markers of metabolic dysfunction. This study aimed to determine whether irregular menstrual cycles (MC) in reproductive-age women is associated with the weight of their daughters at birth and growth up to age five. We studied 4863 pregnant women with menstrual history data in a prospective cohort recruited from the Kaiser Health Plan (1959–1966). Serial measures of their daughters' weight and height were abstracted from medical records. We used analysis of covariance, stratified by maternal BMI, to explore the association between maternal MC and infant birth weight (BW). We included 4774 daughters in a repeated measures analysis to compare the effect of maternal MC on childhood weight through age five. Daughters of non-obese women with irregular MC had a statistically significant lower BW compared to daughters of women with regular MC; this difference was notably amplified among obese women. The daughters' weights were not statistically different when growth was assessed from birth to 5 years. We conclude that daughters of obese women with irregular MC, in particular, had significantly lower BW compared to daughters of women with regular MC, which did not persist over 5 years of follow-up.

Keywords

menstrual irregularity; birth weight

INTRODUCTION

Large well-established, observational studies have shown an association between irregular menstrual cycles (MC) and outcomes of type 2 diabetes mellitus [1] and coronary heart

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disease [2, 3], citing polycystic ovary syndrome (PCOS) as the most likely pathway. Among healthy reproductive-aged women, PCOS may account for up to 70% of women with irregular MC [4, 5].

Although metabolic and reproductive phenotypes among first degree relatives of polycystic ovary syndrome (PCOS) probands have been well-characterized [6–9], limited studies exist on the offspring of PCOS women. Such studies have focused on pregnancy outcomes such as birth weight [10], cognitive development [11], and markers of metabolic abnormalities in prepubertal and pubertal daughters[12, 13]. To our knowledge, there are no longitudinal studies evaluating these daughters. Since the effects of intrauterine life have been implicated in the origin of PCOS [14], evaluation of fetal and early childhood growth may provide insight into the onset of metabolic abnormalities.

Using data from a large population-based cohort of pregnant women and their daughters from the East Bay Area of California (1959–1967), we aim to determine whether maternal menstrual irregularity is independently associated with the weight of daughters at birth and up to five years of age. Given the known association between PCOS and obesity, we hypothesized that maternal body mass index (BMI) would play a role in birth weight.

Methods

Study Design and Sample

The Child Health and Development Studies (CHDS) were initiated in 1959 to investigate events of pregnancy and childhood development [15]. Women were invited to enroll in the CHDS when they contacted participating Kaiser Facilities in the San Francisco Bay Area regarding a confirmed pregnancy. Recruitment efforts from 1959–1966 led to enrollment of 15,528 women, accounting for over 98% of eligible women. Baseline demographic and pregnancy history information was collected by in-person interviews. Information about maternal medical conditions was abstracted from medical records. Active follow-up of the cohort continued until 1972. The institutional review board approved the study protocol and consent according to the standard of the time was obtained from all participants.

Given that prior studies showed early metabolic derangements in prepubertal and pubertal daughters of PCOS women [12, 13], the present investigation focused on 4863 women and their daughters with complete covariate data. Participants were limited to women who delivered liveborn singletons between 22 and 44 gestational weeks. Women with BMI <18.5 kg/m^2 were excluded as they may represent a different subgroup with irregular menstrual cycles due to hypothalamic etiology. Participants were also excluded if they had a diagnosis of diabetes since maternal diabetes is a known risk factor for macrosomia [16].

Maternal data

We previously described the determination of menstrual cycle (MC) pattern in the CHDS participants [3]. Briefly, MC pattern was assessed at baseline according to 1) self-report at the interview and 2) physician report and diagnosis from medical record abstraction.

Maternal race was categorized as Caucasian, African-American, Latino, Asian, or other. Tobacco use was categorized as active use or past/never use. Weight and height were measured at the first interview. Weight was adjusted to compensate for variation in gestational age at measurement by regressing weight on gestational age using locally weighted scatterplot smoothing as previously described [3, 17]. Maternal weight gain was determined as the difference between the last pre-delivery weight and the first recorded weight.

Childhood data

CHDS participants were actively followed during their pregnancy through labor and delivery. Gestational age of the infant was based on the number of completed weeks between date of delivery and the first day of mother's last menstrual period (LMP). At the time of delivery, infant sex was recorded and weight was measured using standardized scales maintained by the study.

Serial measures of weight and height were abstracted from children's medical records for every Kaiser pediatric visit through age five. By the time children reached their fifth birthday, 68% were still Kaiser Health Plan members. Nearly all participants who remained within Kaiser had recorded height and weight data [18].

Statistical analyses

CHDS participants were classified into women with irregular MC and women with regular MC. We stratified our analyses by maternal BMI for three reasons: 1) the known association between PCOS and obesity, 2) the statistical interaction between irregular MC and obesity in our analyses, and 3) in the CHDS cohort, obesity was more prevalent in women with irregular MC. For the birth weight analysis, analysis of covariance (ANCOVA) was used to investigate the relationship between maternal MC and infant birth weight while controlling for maternal age, race, smoking status, pregnancy weight gain, and gestational weeks at time of delivery.

Only daughters with birth weight data and at least one subsequent follow-up growth measurement were included in the childhood growth analysis (n=4774). A repeated measures ANCOVA analysis, with time as a random effect, was used to compare the weight of daughters born to women with irregular MC and the weight of daughters born to women with regular MC over five age intervals – 0–6 months, 6–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years. This analysis was performed using Proc Mixed in SAS 9.2 and was controlled for daughters' height and maternal race. Quadratic time effects were included due to statistical significance.

All analyses were conducted using SAS v9.2.

RESULTS

Of 4863 CHDS mothers, 682 (14.0%) reported irregular MC and 4181 (86.0%) reported regular MC. Compared to women with regular MC, women with irregular MC were on average younger (26.7 ± 5.7 vs. 27.4 ± 6.1, P=0.004) and more likely to be obese (6.6% vs.

5.0%, P=0.08) (Table 1). The two groups of women were not statistically different in terms of active smoking, pregnancy weight gain, and gestational age at delivery.

In the birth weight analysis, daughters of non-obese women with irregular MC had lower BW (−42g) compared to daughters of women with regular MC, after adjusting for possible confounders (3153g vs. 3195g, p=0.02) (Table 2). Daughters of obese women with irregular MC weighed 170g less than daughters of obese women with regular MC (3165g vs. 3335g, p=0.05) (Table 2).

We then explored whether the lower birth weight of daughters born to women with irregular MC persisted over the next five years. Using a repeated measures model with time as a random effect, we assessed the association of maternal MC and serial weights of 4774 daughters with a total of 48,654 observations over five years. Regardless of maternal BMI, there was no significant difference in weight between the two groups of daughters once follow-up weights, adjusted for height and maternal race, were included at five different age intervals – 0–6 months, 6–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years (Table 3). Although not statistically significant, we did note that the daughters of obese women with irregular MC weighed less than daughters of obese women with regular MC up until 12 months, but that after 12 months, the trend was reversed.

DISCUSSION

In this large population-based cohort, we found that daughters of women with irregular MC had a lower birth weight than daughters of women with regular MC. This decrease in birth weight was amplified in the subset of obese women. In the subsequent evaluation of childhood growth between six months and five years of age, however, daughters of women with irregular MC were not statistically different compared to daughters of women with MC regardless of maternal BMI. These results suggest that maternal irregular MC combined with obesity may be associated with a suboptimal *in utero* environment leading to lower birth weight.

Our finding of a lower birth weight in daughters of women with irregular MC is consistent with current literature on the offspring of PCOS women. In a meta-analysis evaluating pregnancy outcome in PCOS women, infants of PCOS women weighed on average 38 grams less than control women [10]. Compared to this meta-analysis, our study further evaluates the effect of maternal obesity, which is important given that associations between PCOS and various metabolic and cardiovascular outcomes have often been complicated by the role of BMI.

Although the mean birth weight of daughters of women with irregular MC is within normal range, the 170g decrease in birth weight noted in daughters of obese women with irregular MC may be clinically significant. We base this on other factors known to decrease birth weight, the most widely studied of which is maternal tobacco use [19]. Just as smoking cessation as a modifiable risk factor is a critical component to prenatal counseling, obesity is also amenable to lifestyle modifications and our results further emphasize the importance of weight loss in women with irregular MC.

A compelling mechanism to explain lower birth weight in cases of maternal irregular MC may be endothelial dysfunction, such as abnormal intima-media thickness of carotid arteries and flow-mediated dilation of brachial arteries, as shown in PCOS women [20, 21]. Palomba et. al. demonstrated that in non-obese infertile PCOS women, uterine, subendometrial, and endometrial blood flow were significantly lower compared to age, BMI-matched controls [22, 23]. In addition, a recent provocative case-control study concluded that endovascular trophoblast invasion was impaired in pregnant PCOS women undergoing termination at 12 weeks gestation compared to health controls [24]. Vascular compromise may subsequently lead to placental insufficiency and lower birth weight infants. Endothelial dysfunction provides a common pathway to lower birth weight infants, as well as increased risk for cardiovascular mortality, which we have previously demonstrated in women with irregular MC in this cohort [3].

The longitudinal growth analysis component of our study, which included growth assessments over five years, indicates that the difference in weight observed at birth does not persist. Although not statistically significant, we did note that the daughters of obese women with irregular cycles weighed less than daughters of obese women with regular cycles up until 12 months, but that after 12 months, the trend was reversed. A prospective cohort study from Sweden has suggested that rapid weight gain during infancy (0–6 months) but not during early childhood (3–6yr) predicted metabolic risk at the 17 years of age [25]. Systematic reviews have also suggested a positive correlation between rapid infancy weight gain and subsequent obesity risk in adulthood [26]. Although our study terminates at five years of age, it provides precursor data to studies on prepubertal and pubertal daughters of PCOS women showing higher levels of triglycerides and 2-hour insulin and lower levels of adiponectin [12, 13], and supports the notion that rapid infant growth may predispose to metabolic risk.

This study has several limitations. First, the study population was recruited between 1959–1967 and the prevalence of maternal obesity in the cohort was 4.9%, significantly less than the contemporary prevalence of 22.0% in the United States [27]. We address this issue of generalizability by providing results stratified by maternal BMI. However, we believe that our cohort provides a unique opportunity to examine a large group of non-obese women with irregular cycles, which may be relevant in other countries with a lower overall prevalence of obesity. Furthermore, these daughters are now in their fifth decades of life and may provide invaluable longitudinal data on cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia.

Limitations of our study include the fact that our exposed group of women with irregular MC was not formally diagnosed with PCOS. This group of women with irregular MC likely includes etiologies other than PCOS. This is evident in the fact that the prevalence of irregular MC in this cohort was 14%, which is higher than the accepted 5–8% prevalence of PCOS. We attempted to exclude women with hypothalamic amenorrhea by imposing a BMI cut-off of 18.5 kg/m^2. Furthermore, it is possible that a selection bias may exist since these women with irregular MC were able to conceive at a time in which options for assisted conceptions would have been limited. The strengths of our study include the large ethnically

diverse cohort of pregnant women and prospective identification of women with irregular MC with subsequent longitudinal follow-up of the daughters over five years.

In conclusion, daughters of obese women with irregular menstrual cycles have a significant decrease in birth weight compared to daughters of obese women with regular menstrual cycle. This difference no longer exists by 6 months of age and through early childhood, suggesting the possibility of rapid growth in infancy in this subset of girls which may portend future metabolic risk.

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Table 1

Baseline characteristics of the CHDS cohort (N=4863)

	Irregular menstrual cycles (N=682)	Regular menstrual cycles (N=4181)	P-value
Maternal age, y	26.7 ± 5.7	27.4 ± 6.1	0.004
Maternal BMI ≥30 kg/m^2, n (%)	45 (6.6)	209 (5.0)	0.08
Maternal race			0.70
Caucasian, n (%)	474 (69.5)	2846 (68.1)	
African-American, n (%)	151 (22.1)	925 (22.1)	
Latino, n(%)	18 (2.6)	134 (3.2)	
Asian, n (%)	22 (3.2)	135 (3.2)	
Other, n (%)	17 (2.5)	141 (3.4)	
Active smoker, n (%)	258 (37.8)	1446 (34.6)	0.10
Pregnancy weight gain, kg	9.4 ± 3.7	9.4 ± 3.6	0.62
Gestational age at delivery, weeks	39.8 ± 2.4	39.6 ± 2.1	0.12

Continuous variables – mean ± SD; categorical variables – n (%)

Table 2

Birth weight of daughters of CHDS cohort stratified by maternal menstrual cycle (MC) and maternal BMI

	Maternal BMI <30 kg/m^2	**Maternal BMI ≥ 30 kg/m^2**
Maternal irregular MC	3153 (3114, 3193)[a, b]	3165 (2939, 3390)
Maternal regular MC	3195 (3169, 3220)	3335 (3157, 3512)
Difference in birth weight, grams[c]	−42	−170
P-value	0.02	0.05

[a] Mean birth weight in grams (95% confidence interval)

[b] Analyses adjusted for maternal age, maternal race, maternal smoking, pregnancy weight gain, and gestational age

[c] Difference in birth weight of infants born to mothers with irregular cycles compared to infants born to mothers with regular cycles

Table 3

Mean difference in weight (grams ± standard deviation) over five years of daughters born to women with irregular menstrual cycles compared to daughters born to women with regular menstrual cycles

Age interval of daughters	Maternal BMI <30 kg/m^2		Maternal BMI ≥ 30kg/m^2	
	Weight difference (grams)[a, b]	P-value	Weight difference (grams)	P-value
0–6 months	−13 ± 39	0.74	−109 ± 82	0.18
6–12 months	−11 ± 58	0.85	−165 ± 172	0.34
1–2 years	−8 ± 86	0.92	166 ± 236	0.48
2–3 years	102 ± 122	0.40	219 ± 308	0.48
3–4 years	97 ± 151	0.52	75 ± 388	0.85
4–5 years	4 ± 167	0.98	214 ± 449	0.63

[a] Difference in weight comparing daughters of mothers with irregular cycles to daughters of mothers with regular cycles

[b] Analyses adjusted for height and maternal race