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What factors are related to recurrent preterm birth among underweight women?

Anna I Girsen, MD PhD¹, Jonathan A Mayo, MPH², Matthew B Wallenstein, MD², Jeffrey B Gould, MD², Suzan L Carmichael, PhD², David K Stevenson, MD², Deirdre J Lyell, MD², and Gary M Shaw, DrPH²

¹Department of Obstetrics & Gynecology, Stanford University School of Medicine, Stanford, CA

²March of Dimes Prematurity Research Center, Division of Developmental & Neonatal Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford CA.

Abstract

Objective: Our objective was to identify factors associated with recurrent preterm birth among underweight women.

Methods: Maternally-linked hospital and birth certificate records of deliveries in California between 2007–2010 were used. Consecutive singleton pregnancies of women with underweight body mass index (BMI <18.5 kg/m²) in the first pregnancy were analyzed. Pregnancies were categorized based on outcome of the first and second birth as: term-term; term-preterm; preterm-term and preterm-preterm.

Results: We analyzed 4,971 women with underweight BMI in the first pregnancy. Of these, 670 had at least one preterm birth. Among these 670, 86 (21.8%) women experienced a recurrent preterm birth. Odds for first term - second preterm birth were decreased for increases in maternal age (aOR:0.90,95%CI:0.95–0.99) whereas interpregnancy interval <6 months was related to both first term - second preterm birth (aOR: 1.66,95%CI: 1.21–2.28) and first preterm birth - second term birth (aOR: 1.43,95%CI: 1.04–1.96). Factors associated with recurrent preterm birth were: negative or no change in pre-pregnancy weight between pregnancies (aOR: 1.67,95%CI: 1.07–2.60), inter-pregnancy interval <6 months (aOR:2.14,95%CI: 1.29–3.56), and maternal age in the first pregnancy (aOR:0.93,95%CI:0.90–0.97).

Conclusions: Recurrent preterm birth among underweight women was associated with younger age, short inter-pregnancy interval, and negative or no weight change between pregnancies.

Keywords

preterm birth; high risk pregnancy; recurrence; underweight; body mass index; inter-pregnancy interval

Corresponding Author: Anna I Girsen, MD PhD, Address: Department of Obstetrics & Gynecology, HH333 MC 5317 300 Pasteur Dr., Stanford CA 94305, Phone: +1 (650) 460 4902, agirsen@stanford.edu, Fax: (650) 723-7737.

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Introduction

Each year more than 450,000 preterm infants are born in the United States at less than 37 weeks of gestation [1]. In addition to major morbidity and mortality in the neonatal period [2], preterm birth (PTB) is associated with significant long-term morbidity and high economic costs for the society [2,3].

Although there is a known association between maternal pre-pregnancy underweight and increased risk of PTB [4–8], the risk factors for recurrent PTB specifically among women who have underweight BMI in their first pregnancy remain unclear. Previous studies on recurrent PTB are done among women in all body mass index (BMI) categories [5] and have not specified the factors related to recurrent PTB among underweight women. Among women in all BMI categories, the factors related to recurrent PTB include a decrease from normal to underweight prepregnancy BMI between pregnancies [5], a short inter-pregnancy interval (IPI), history of prior PTB at 28–32 weeks gestation and younger maternal age. Identification of potentially modifiable risk factors specific to women with low BMI could help in counseling underweight women who have experienced a PTB.

Our objective therefore was to identify factors associated with recurrent PTB among underweight women (BMI <18.5) taking into account potential effects of severity (i.e., narrower categories of BMI such as <16) of underweight.

Methods

This is a retrospective cohort study performed using the California birth cohorts from 2007–10, which link California birth records with Office of Statewide Health and Planning maternal and infant hospital discharge data. The datasets include maternal and pregnancy characteristics from birth certificates combined with clinical details from birth hospitalization and link multiple births to the same mother. The dataset has been previously described in more detail [9]. Before its initiation, Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects reviewed and approved this study (project #24543, approval date 11/18/2014).

Maternal demographics are based on birth certificate data. Variables included in analyses were maternal age, maternal height, maternal pre-pregnancy weight in the first and second pregnancy, race/ethnicity, month of prenatal care initiation, payer for the delivery, gestational age, and inter-pregnancy interval. Maternal comorbidities in the form of *International Classification of Diseases, 9th revision, Clinical Modification (ICD- 9-CM)* diagnoses were identified from birth hospitalization data. PTB was defined as a live birth occurring at less than 37 weeks of gestation. Information on gestational age at delivery was based on obstetric estimate provided on the birth certificate. PTB was subtyped based on maternal ICD-9-CM diagnosis and procedure codes along with birth certificate codes in a hierarchical classification. First, spontaneous PTBs were identified as those births <37 weeks with preterm premature rupture of membranes, premature labor, or tocolytics. Medically indicated PTBs were those induced or delivered by cesarean section <37 weeks and not previously identified as spontaneous. All births <37 weeks not captured by either above

groups were considered unknown. Maternal BMI was calculated based on height and prepregnancy weight ($\text{BMI} = \text{weight (in kilograms)} / \text{height}^2 \text{ (in meters)}$). Underweight BMI was defined as $<18.5 \text{ kg/m}^2$ and further categorized into severe ($<16 \text{ kg/m}^2$) or moderate underweight ($16\text{--}16.9 \text{ kg/m}^2$) and mild underweight ($17\text{--}18.49 \text{ kg/m}^2$) [10]. Data on maternal prepregnancy weight and height were self-reported.

We restricted our analyses to women who had underweight BMI in their first pregnancy and had a singleton live birth in the subsequent pregnancy between 2007 and 2010. To establish the occurrence of recurrent PTB among women with normal BMI, we analyzed 54,895 women with two consecutive live births and normal BMI at the time of the first pregnancy. To ensure correct identification of consecutive births to the same woman, we required that the maternal birth date match across records and that the month and year of the preceding birth listed on the second birth certificate matched the month and year of birth recorded on the first birth certificate.

Between 2007 and 2010, there were 106,732 women who delivered their first and second singleton live births in California. First we removed 13,022 women with missing or outlier height (<135.62 or $>196.58 \text{ cm}$) or prepregnancy weight (<34.02 or $>204.12 \text{ kg}$) in either pregnancy. Next we identified 5222 (5%) women who had an underweight prepregnancy BMI in their first pregnancy. We then sequentially excluded women with missing or outlier (<20 or >42 weeks) gestation in either pregnancy ($n=67$) or difference in reported height ($>12.7 \text{ cm}$) across pregnancies ($n=184$), and were left with an analytic base of 4971 women. The study population was categorized into outcome groups based on the first and the second birth as: term-term; term-preterm; preterm-term and preterm-preterm. The primary outcome of study was recurrent preterm birth and recurrent term birth was used as the reference. Weight change between pregnancies was calculated by subtracting pre-pregnancy weight in the first pregnancy from pre-pregnancy weight in the second pregnancy.

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Comparisons between two groups were performed using Student's *t*-test for continuous variables and with Chi-squared test for categorical variables. For multivariable models, covariates were chosen based on prior knowledge for their impact on PTB. Covariates included were: severity of underweight in the first pregnancy (mild, moderate/severe), weight change between pregnancies (weight gain/negative or no weight gain), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Asian, Hispanic, Other), maternal education in the second pregnancy (high school diploma, some high school or less, some college, college graduate or more, unknown/unreported), prenatal care initiation (during first 5 months, 6 months or later/no initiation/unknown), payer for the delivery (Medi-Cal, private, NA/uninsured/unknown, other), inter-pregnancy interval (less than 6 months, 6 months or greater), maternal age (continuous) and maternal height (continuous) to reduce further potential residual confounding associated with the BMI algorithm [11]. Associations between factors and the three outcomes of term-PTB, PTB-term or recurrent PTB (vs. recurrent term birth) were estimated using backward elimination logistic regression and their adjusted odds ratios (aOR) and 95% confidence intervals [CIs]. $P<0.05$ was considered statistically significant for covariate retention in the models.

Results

Of the 4971 women with underweight BMI in their first pregnancy, 86 women (1.7%) had a recurrent PTB compared to 778 (1.4%) among women with normal pre-pregnancy BMI in their first pregnancy ($p=0.077$). Characteristics of the study population by birth outcome are presented in Table 1. Underweight women with recurrent PTB were significantly younger (age <20 years: 38.4% vs. 20.4% in term-term group, $p<0.001$), more likely to have public insurance (Medi-Cal) (46.5% vs. 34.8%, $p=0.01$), and more likely to have an inter-pregnancy interval of less than 6 months (25.6% vs. 11.8%, $p<0.001$) compared to underweight women with recurrent term birth (Table 1). After excluding cases with indicated PTB from the analysis, the maternal and obstetric characteristics remained unchanged (data not shown).

Among underweight women with PTB in the first pregnancy, 21.8% experienced a recurrent PTB. The factors related to increased odds for recurrent PTB compared to recurrent term birth were negative or no weight change between pregnancies (aOR: 1.67, 95%CI: 1.07 – 2.60) and inter-pregnancy interval of less than 6 months (aOR: 2.14, 95%CI: 1.29 – 3.56), while increase in maternal age was related to decreased odds of recurrent PTB (aOR: 0.93, 95%CI: 0.90 – 0.97) (Table 2).

In multivariable modeling, odds for first term birth - second PTB were decreased for increases in maternal age (adjusted odds ratio, aOR: 0.90 per one-year increase in age, 95%CI: 0.95 – 0.99) and increased for inter-pregnancy interval of less than 6 months (aOR: 1.66, 95%CI: 1.21 – 2.28) (Table 2). Increased odds of first PTB with second term birth was related to inter-pregnancy intervals of less than 6 months (aOR: 1.43, 95%CI: 1.04 – 1.96), whereas, Asian compared to Non-Hispanic White race/ethnicity was related to decreased odds of first PTB with second term birth (aOR: 0.65, 95%CI: 0.46 – 0.90) (Table 2). After removing indicated PTBs from analyses, results from the multivariable modeling remained largely unchanged except the weight change between pregnancies was no longer a significant predictor for recurrent spontaneous PTB (data not shown). In addition, after removing cases with maternal co-morbidities (any pre-existing or gestational hypertension, diabetes or preeclampsia in pregnancy 1 or pregnancy 2) the results of the multivariable modeling remained largely the same except maternal age, height and IPI were no longer significant predictors for the outcome of PTB-Term but maternal education (some high school or less vs. high school diploma) was associated with PTB-Term outcome (OR: 1.37, 95%CI:0.93–2.01) (data not shown).

Discussion

We analyzed almost 5,000 consecutive live births of women with pre-pregnancy underweight (i.e., BMI <18.5) in the first pregnancy and found that the factors associated with increased odds of recurrent PTB were weight reduction or no weight change between pregnancies, inter-pregnancy interval of less than 6 months, and decreased odds of recurrent PTB with younger maternal age. However, recurrence percentages between women with normal pre-pregnancy BMI, 1.4%, compared to women with underweight BMI, 1.7%, were not substantially different. By examining specific factors related to recurrent preterm birth

among women with different severity of underweight, this study adds to the existing literature that has not looked at specifically the underweight women. In addition, our study has clinical implications for counseling underweight women who have experienced a PTB.

Although several studies have shown an association between maternal prepregnancy underweight and increased risk of PTB [6, 7, 12], only a few studies have investigated maternal underweight and the risk of recurrent PTB [5, 8]. In their historical cohort of multiparous women in Utah, Simonsen *et al.* also found that maternal underweight (BMI <18.5 kg/m²) compared to normal weight (BMI 18.5–24.9 kg/m²) was related to an increased risk of recurrent PTB in the second and third live birth [8]. In another study, Whiteman *et al.* studied recurrent live births across all the BMI categories and demonstrated that PTB occurred most often among women who lowered their weight from normal to underweight (5), whereas, no significant risk for PTB among women who were underweight in both pregnancies was noted. Neither Whiteman *et al.* or Simonsen *et al.* examined the severity of underweight related to recurrent PTB or the specific factors related to recurrent PTB among underweight women as we did in the current study. In this study cohort, overall recurrence of PTB among underweight women with prior PTB was 21.8%. Although, women with prior PTB have been shown to be at increased risk of recurrence compared to women with prior term birth [13,14], a history of PTB only explains the associated risks of a small amount (~10%) of PTBs [14]. Thus, identifying other factors related to recurrent PTB could prove valuable for prematurity prevention.

In this study, we investigated the difference in pre-pregnancy weights between pregnancies and noted that no change or a negative weight change between pregnancies was associated with a significantly increased risk of recurrent PTB among underweight women. Our finding is in line with prior studies that have demonstrated that recurrent PTB is related to less than appropriate gestational weight gain [8] and a change from normal to underweight BMI category between pregnancies [5]. That is, underweight women who do not gain weight during pregnancies are at the highest risk of recurrent PTB. However, the association between BMI and PTB remains unclear [15]. Although the underlying mechanisms related to PTB among underweight women are not fully understood, factors like eating disorders [16], decreased micronutrient intake [17] and increased stress and anxiety levels [18] have been postulated to play a role.

The strongest factor related to recurrent PTB among underweight women was IPI of less than six months. Our finding is consistent with prior work where IPI of less than six months was associated with increased risk of recurrent PTB across all BMI categories [18]. In addition, Whiteman *et al.* demonstrated that underweight mothers had significantly shorter IPIs compared to other BMI categories, although they did not test the association between short IPI and PTB or recurrent PTB [5]. The association between short IPI and PTB may be associated with maternal micronutrient depletion, in particular folate depletion [19]. Interestingly, in our study a short IPI was also associated with increased risks for women whose first birth was term and second was preterm, as well as the reverse (first birth preterm and second term), although risks of short IPI were highest among women with recurrent PTB and a PTB after a term birth. It is possible that women with short IPI were unable to

change their weight in between the pregnancies and remained it a higher risk because of their starting pre-pregnancy weight.

Our study has both strengths and limitations. Because of its large size, we were able to examine consecutive live births of underweight women taking maternal underweight categories and different birth outcomes into account. In addition, the more recent cohort in our study and the population-based data employed increased the generalizability of our findings. However, we were limited to data derived from birth certificates and hospital discharge databases, which are not always reliable. In addition, we were limited to use of self-reported weight and height in BMI calculations, although associations between self-reported BMI and pregnancy outcomes may be a slightly overestimated [20]. Although BMI is a simple index of weight-for-height that is commonly used to classify underweight it may not correspond to the same degree of thinness in different populations due, in part, to different body proportions. Furthermore, although we did have self-reported data on maternal pre-pregnancy and delivery weights, we did not include gestational weight gain in the analysis because these values would have not presented a true pregnancy weight gain which is non-linear and dependent on gestational age at delivery. It is also likely that our study was not sufficiently powered to detect differences in behavioral factors like eating disorder and we were not able to account for the effect of other rare pregnancy complications that might have caused PTB. Previously, behavioral factors including eating disorders have been shown to be poorly recorded in large population cohorts [21] and, thus, may not reflect the true occurrence of these disorders in the cohort. Finally, our large-scale study cannot identify specific mechanisms underlying the association between maternal underweight and recurrent preterm birth, but, importantly, may offer background for more specific, mechanistic studies.

In conclusion, we found that recurrent PTB among underweight women was associated with younger age, IPI less than six months and negative or no weight change between pregnancies. Our results support counseling underweight women who experience PTB about the potential benefits of an adequate inter-pregnancy-interval.

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Demographics and the obstetrical characteristics of women with consecutive pregnancies and underweight body mass index (BMI <18.5 kg/m2) in the first pregnancy.

Table 1.

	Recurrent term birth N=4301	Term-PTB N=275	P-value*	PTB-Term N=309	P-value*	Recurrent PTB N=86	P-value*	Total N= 4971
Pre-pregnancy BMI, pregnancy 1	n (column %)		0.22		0.26		0.35	
	Severe/Moderate underweight	58 (21.1)		64 (20.7)		19 (22.1)		922
	Mild underweight	217 (78.9)		245 (79.3)		67 (77.9)		4049
Pre-pregnancy BMI, pregnancy 2			0.20		0.28		0.34	
	Severe/Moderate underweight	39 (14.2)		42 (13.6)		13 (15.1)		524
	Mild underweight	106 (38.5)		119 (38.5)		33 (38.4)		1887
	Normal	124 (45.1)		142 (46.0)		40 (46.5)		2441
	Overweight	4 (1.5)		4 (1.3)				91
	Obese	2 (0.7)		2 (0.6)				28
Change in prepregnancy weights								
	Weighed same or less at beginning of pregnancy 2 than pregnancy 1	91 (33.1)	0.46	96 (31.1)	0.96	34 (39.5)	0.09	1552
	Weighed more at beginning of pregnancy 2 than pregnancy 1	184 (66.9)		213 (68.9)		52 (60.5)		3419
Maternal age, pregnancy 1			0.01		0.007		<0.001	
	<20	80 (29.1)		84 (27.2)		33 (38.4)		1075
	20–24	67 (24.4)		75 (24.3)		26 (30.2)		1210
	25–29	60 (21.8)		73 (23.6)		10 (11.6)		1240
	30–34	52 (18.9)		50 (16.2)		13 (15.1)		1104
	35	16 (5.8)		27 (8.7)		4 (4.7)		342
Race/Ethnicity			0.31		0.04		0.06	
	Non-Hispanic White	90 (32.7)		107 (34.6)		26 (30.2)		1662
	Non-Hispanic Black	19 (6.9)		20 (6.5)		6 (7.0)		228
	Asian	79 (28.7)		71 (23.0)		17 (19.8)		1450
	Hispanic	69 (25.1)		87 (28.2)		33 (38.4)		1335
	Other/unknown	18 (6.5)		24 (7.8)		4 (4.7)		296
Prenatal care initiation, pregnancy 1			0.23		0.05		0.07	

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		Recurrent term birth N=4301	Term-PTB N=275	P-value*	PTB-Term N=309	P-value*	Recurrent PTB N=86	P-value*	Total N= 4971
	Initiation in first 5 months	4089 (95.1)	257 (93.5)		286 (92.6)		78 (90.7)		4710
	Initiation 6 months or later/No initiation/Unknown	212 (4.9)	18 (6.5)		23 (7.4)		8 (9.3)		261
Payer for prenatal care, pregnancy 1				0.04		0.04		0.01	
	MediCal (Public)	1495 (34.8)	119 (43.3)		125 (40.5)		40 (46.5)		1779
	Private	2612 (60.7)	144 (52.4)		172 (55.7)		40 (46.5)		2968
	NA/Uninsured/Unknown	68 (1.6)	4 (1.5)		4 (1.3)		4 (4.7)		80
	Other	126 (2.9)	8 (2.9)		8 (2.6)		2 (2.3)		144
Maternal education, pregnancy 2	Some high school or less	490 (11.4)	45 (16.4)	0.03	51 (16.5)	0.02	15 (17.4)	0.10	601
	High school diploma/GED	1048 (24.4)	75 (27.3)		83 (26.9)		26 (30.2)		1232
	Some college	1002 (23.3)	65 (23.6)		68 (22.0)		21 (24.4)		1156
	College graduate or more	1609 (37.4)	82 (29.8)		101 (32.7)		21 (24.4)		1813
	Missing	152 (3.5)	8 (2.9)		6 (1.9)		3 (3.5)		169
Inter-pregnancy interval				<0.001		0.01		<0.001	
	Less than 6 months	508 (11.8)	54 (19.6)		51 (16.5)		22 (25.6)		635
	6 months or greater	3793 (88.2)	221 (80.4)		258 (83.5)		64 (74.4)		4336
PTB subtype, pregnancy 1									
	PPROM				68 (22.0)		17 (19.8)		85
	Spontaneous				161 (52.1)		56 (65.1)		217
	Indicated						9 (10.5)		64
	Unknown				25 (8.1)		4 (4.7)		29
Gestational weeks at delivery, pregnancy 1									
	20–23 weeks				4 (1.3)		1 (1.2)		5
	24–27 weeks				10 (3.2)		3 (3.5)		13
	28–31 weeks				14 (4.5)		10 (11.6)		24
	32–36 weeks				281 (90.9)		72 (83.7)		353
	37–42 weeks	4301 (100)	275 (100)						4576
PTB subtype, pregnancy 2									
	PPROM		55 (20.0)				12 (14.0)		67
	Spontaneous		151 (54.9)				53 (61.6)		204

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		Recurrent term birth N=4301	Term-PTB N=275	P-value*	PTB-Term N=309	P-value*	Recurrent PTB N=86	P-value*	Total N= 4971
			43 (15.6)				11 (12.8)		54
	Indicated		26 (9.5)				10 (11.6)		36
	Unknown								
Gestational weeks at delivery, pregnancy 2									
	20–23 weeks		2 (0.7)						2
	24–27 weeks		6 (2.2)				7 (8.1)		13
	28–31 weeks		19 (6.9)				8 (9.3)		27
	32–36 weeks		248 (90.2)				71 (82.6)		319
	37–42 weeks	4301 (100)			309 (100)				

* By chi-squared test vs. recurrent term birth Data are presented as n (%) or mean (SD) PTB, preterm birth; BMI, body mass index

Table 2.

Factors related to outcomes of recurrent preterm birth, term birth - preterm birth and preterm birth - term birth compared to recurrent term birth among women with underweight BMI in the first pregnancy.

Outcome ^a	Adjusted OR ^{a,b}	95% CI
Recurrent preterm birth		
Change in pre-pregnancy weights ^a .		
Weighed more at beginning of pregnancy 2 than pregnancy 1	Reference	
Weighed same or less at beginning of pregnancy 2 than pregnancy 1	1.67	1.07–2.60
Maternal height ^c	0.91	0.84–0.99
Maternal age in pregnancy 1 ^d	0.93	0.90–0.97
Inter-pregnancy interval: 6 months <6 months	Reference 2.14	1.29–3.56
Term birth - preterm birth		
Maternal age in pregnancy 1 ^d	0.97	0.95–0.99
Inter-pregnancy interval: 6 months <6 months	Reference 1.66	1.21–2.28
Preterm birth - term birth		
Maternal height ^c	0.95	0.91–0.99
Race/ethnicity:		
Non-Hispanic White	Reference	
Asian	0.65	0.46–0.90
Hispanic	0.90	0.66–1.22
Non-Hispanic Black	1.40	0.85–2.32
Other/unknown	1.15	0.72–1.85
Inter-pregnancy interval: 6 months <6 months	Reference 1.43	1.04–1.96

^a Recurrent term birth was a reference

^b Model was built by backward step-wise exclusion (stay in criterion $p < 0.05$) from the initial model that included following covariates: payer of the delivery; initiation of prenatal care; underweight category in pregnancy 1, maternal education in the second pregnancy, and race/ethnicity.

^c Odds calculated for per-unit (inch) increase in height

^d Odds calculated for per-unit (year) increase in age OR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; PTB, preterm birth