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## Spontaneous and indicated preterm delivery risk is increased among overweight and obese women without prepregnancy chronic disease

Sung Soo KIM<sup>a,c</sup>, Pauline MENDOLA<sup>a</sup>, Yeyi ZHU<sup>a,d</sup>, Beom Seuk HWANG<sup>b,e</sup>, and Katherine L. GRANTZ<sup>a</sup>

<sup>a</sup>Epidemiology, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Rockville, MD

<sup>b</sup>Biostatistics and Bioinformatics Branches, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Rockville, MD

<sup>c</sup>Division of Epidemiology and Health Index, Korea National Research Institute of Health, Osong, Korea

<sup>d</sup>Division of Research, Kaiser Permanente Northern California, Oakland, CA

<sup>e</sup>Department of Applied Statistics, Chung-Ang University, Seoul, Korea

### Abstract

**Objective**—To investigate the independent impact of prepregnancy obesity on preterm delivery among women without chronic diseases by gestational age, preterm category and parity.

**Design**—A retrospective cohort study.

**Setting**—Data from the Consortium on Safe Labor (CSL) in the U.S. (2002–2008).

**Population**—Singleton deliveries at ≥ 23 weeks of gestation in the CSL (43,200 nulliparas and 63,129 multiparas) with a prepregnancy body mass index (BMI) ≥ 18.5kg/m<sup>2</sup> and without chronic diseases.

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Address correspondence to Katherine L. Grantz, M.D., M.S., Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6710B Rockledge Drive Room 3124, MSC 7004, Bethesda, MD 20817 USA. Telephone: (301) 435-6935. Katherine.grantz@nih.gov.

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**Disclosure of Interests** The authors report no conflict of interest. The ICMJE disclosure forms are available as online supporting information.

**Contribution to Authorship** S.S. Kim, K.L. Grantz and P. Mendola conceived the study concept and design. S.S. Kim completed the analysis, including quality assurance and control, with the assistance of Y. Zhu and B.S. Hwang and wrote the manuscript under the supervision of K.L. Grantz. All authors aided in the design of the study, in the interpretation of the data and critical revision of the manuscript for important intellectual content, and all authors approved the final version.

**Detailed of Ethics Approval** The CSL was approved by the institutional review boards of all participating institutions (listed in the Acknowledgements) and the NIH IRB #3854 was obtained on 9/12/2007.

**Methods**—Association of prepregnancy BMI and the risk of preterm delivery was examined using Poisson regression with normal weight as reference.

**Main outcome measures**—Preterm deliveries were categorized by gestational age (extremely, very, moderate to late) and category (spontaneous, indicated, no recorded indication).

**Results**—Relative risk of spontaneous preterm delivery was increased for extremely preterm among obese nulliparas (1.26; 95% CI, 0.94–1.70 for overweight, 1.88; 95% CI, 1.30–2.71 for obese class I, 1.99; 95% CI, 1.32–3.01 for obese class II/III) and decreased for moderate to late preterm delivery among overweight and obese multiparas (0.90; 95% CI, 0.83–0.97 for overweight, 0.87; 95% CI, 0.78–0.97 for obese class I, 0.79; 95% CI, 0.69–0.90 for obese class II/III). Indicated preterm delivery risk was increased with prepregnancy BMI in a dose-response manner for extremely preterm and moderate to late preterm among nulliparas, as were for moderate to late preterm delivery among multiparas.

**Conclusions**—Pregnancy BMI was associated with increased risk of preterm delivery even in the absence of chronic diseases, but the association was heterogeneous by preterm categories, gestational age and parity.

### Keywords

pregnancy obesity; pregnancy; preterm delivery; spontaneous delivery; medically-indicated delivery; obesity

## Introduction

Preterm delivery is the leading cause of infant mortality and preterm infants are at substantially elevated risk of developing neonatal and long-term complications.<sup>1</sup> Preterm delivery in the United States accounted for 9.8% of deliveries at 24 weeks or later in 2010.<sup>2</sup> Even though the death rate among extremely premature infants has recently declined,<sup>3</sup> 67% of U.S. infant deaths occurred among preterm infants in 2010.<sup>4</sup>

Maternal obesity has been associated with a wide range of adverse obstetric and neonatal outcomes,<sup>5–9</sup> however, the association between prepregnancy obesity and preterm delivery varies in part due to differences in how preterm delivery etiological category (spontaneous versus indicated), gestational age at delivery and parity have been dealt with in prior studies. A recent meta-analysis<sup>10</sup> reported 33% and 83% higher risk for preterm delivery among obese class II and III women, respectively and a progressively higher risk of 43–127% for very preterm delivery before 32 weeks of gestation among obese class I, II and III women. However, a decreased risk of spontaneous preterm delivery among overweight or obese class I women was also observed and insufficient data on etiological and gestational age categories of preterm deliveries, high degrees of heterogeneity, and limited covariate adjustment among the abstracted studies were noted.<sup>10</sup> Nulliparous women are at greater risk than multiparous women for overall preterm delivery and both spontaneous and indicated category.<sup>11</sup> In a U.S. study<sup>12</sup> based on birth certificate data in Florida, the risks of extremely, very, and overall preterm delivery were highest among nulliparous obese women compared with multiparous non-obese women. In other studies, women with prepregnancy chronic conditions, such as hypertension, diabetes, asthma and renal disease, in particular

were at elevated risk of preterm delivery.<sup>13–15</sup> Therefore, to explore the potential independent association between maternal obesity and preterm delivery, it is essential to untangle the impact of obesity from that of preexisting co-morbidity which may be weight-related and consider subgroup characteristics, such as parity. Our objective was to investigate preterm delivery risk associated with prepregnancy BMI among women without chronic diseases by etiological and gestational age category, and parity in a large, contemporary U.S. cohort.

## Methods

The Consortium on Safe Labor (CSL) was a retrospective cohort of deliveries at ≥ 23 weeks from 19 hospitals in the U.S. (2002–2008). Details of the cohort have been described elsewhere.<sup>16</sup> In brief, maternal demographic characteristics, medical, reproductive, and prenatal history, intrapartum interventions, postpartum complications and neonatal characteristics were extracted from hospital delivery admission electronic medical records and discharge summaries. International Classification of Diseases, Ninth Revision (ICD-9) codes were abstracted for both mothers and infants. The CSL was approved by the institutional review boards of all participating institutions (listed in the Acknowledgements).

Among 223,394 singleton deliveries in the CSL, 148,469 (66%) had both maternal prepregnancy weight and height information available to calculate BMI (kg/m<sup>2</sup>). Women were excluded from this analysis if they had pre-existing chronic diseases including hypertension, diabetes, asthma, depression, human immunodeficiency virus infection and gastrointestinal, renal, heart, or thyroid disease recorded in their medical record or by ICD-9 code (n=29,273), as were the 6,822 deliveries to underweight women (BMI <18.5) and 65 deliveries with missing maternal age. One site that did not report indications for induction was also excluded (n=5,980). The final sample for the main analyses was 106,329 deliveries among 100,849 women and 95% of women contributed only one pregnancy.

Maternal prepregnancy BMI was classified into four groups: normal (BMI 18.5–24.9), overweight (25–29.9), obese class I (30–34.9) and obese class II/III (≥ 35). Gestational age at preterm deliveries were categorized as extremely (23–27 completed weeks), very (28–31 weeks), and moderate to late preterm (32–36 weeks).<sup>17</sup> We defined categories of preterm deliveries as follows: spontaneous delivery including spontaneous labor and preterm premature rupture of the membranes (PPROM); indicated delivery; and no recorded indication. These categories were hierarchically classified as previously reported.<sup>18</sup> Women who presented in spontaneous labor were included in the spontaneous labor category even if they had other indications. Women with spontaneous premature rupture of membranes without spontaneous labor were classified as PPRM. If women did not have spontaneous labor or PPRM, other indications of preterm deliveries were considered. Women who had maternal, fetal or obstetric pregnancy complications were grouped into the indicated preterm delivery. The “no recorded indication” category included deliveries reported as elective induction as well as induced labor or cesarean deliveries with no abstracted maternal, fetal or obstetric indications.<sup>18</sup>

Covariates were selected *a priori*: maternal age (continuous), race/ethnicity (White, Black, Hispanic, other/unknown), insurance type (private, public/self-pay, other/unknown), marital status (married, unmarried/unknown), smoking (yes, no/unknown) and alcohol use (yes, no/unknown) during pregnancy, and study site. The delivery was the unit of analysis for all statistical testing. Descriptive statistics included mean and standard deviation or percentages by gestational age category. Significance testing for descriptive statistics used linear or multinomial logistic regression with generalized estimating equations to account for multiple deliveries from the same woman.

Analyses were stratified by parity. We calculated preterm delivery incidence and then performed analyses stratified by gestational age category at delivery and whether the preterm delivery was spontaneous or medically indicated. Lastly, we conducted a sensitivity analysis restricted to women who did not develop gestational hypertensive disorders or gestational diabetes in order to assess the risk of preterm delivery among overweight and obese women who did not develop common pregnancy complications that are associated with increased risk of preterm delivery. Specifically, modified multivariable Poisson regressions with a log link function<sup>19</sup> were fitted to calculate relative risks (RRs) and 95% confidence intervals (CIs) of extremely, very and moderate to late preterm delivery by maternal prepregnancy BMI class stratified by parity, after adjusting for covariates. Generalized estimating equations with a first-order autoregressive covariance structure correlation matrix were used to estimate error variance accounting for multiple pregnancies contributed by the same woman. Test of linear trend was conducted using the median BMI value for each BMI group in the regression models. We also compared preterm precursors for delivery by gestational age category at delivery and parity. Finally, we plotted the proportion of precursors of preterm deliveries by prepregnancy BMI and gestational age category at delivery by parity. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

Among singleton deliveries in the CSL, the percent of women who were White (52% vs 45%) or married (62% vs 52%) were higher and having private insurance (52% vs 63%) was lower among women with BMI data compared with women without BMI data, but there were not clinically meaningful differences with respect to the prevalence of pre-existing chronic diseases (20% for both) and parity (40% vs 39%). Preterm delivery was lower among women with BMI versus without BMI data (10.9% vs 13.4%).

In our sample of 106,329 deliveries among women without prepregnancy chronic disease and with normal BMI or above, 9,938 deliveries (9.3%) were preterm. Rates of extremely, very, and moderate to late preterm deliveries were 0.7%, 1.0% and 7.7%, respectively (Table 1). Mothers who delivered preterm were more likely to be overweight or obese, Black or Hispanic, of unmarried/unknown marital status, have public insurance, be nulliparous and smoke or drink alcohol during pregnancy than women who delivered full term, and the differences tended to be larger the earlier the gestational timing of preterm deliveries ( $p < 0.01$  for all comparisons).

Extremely preterm delivery was increased among overweight or obese nulliparous women compared with women of normal BMI for both spontaneous and indicated deliveries (Table 2), while no increased risk was observed for multiparous women. Among very preterm deliveries, significant associations were only observed for indicated deliveries among nulliparous obese class I and multiparous obese class II/III women. The risks of indicated moderate to late preterm delivery were significantly elevated by the increase of prepregnancy obesity for both nulliparous and multiparous women in a dose-response fashion, while overweight or obese multiparous women had a lower risk for spontaneous moderate to late preterm deliveries.

In a sensitivity analysis restricted to women who did not develop gestational hypertensive disorders or gestational diabetes during pregnancy, nulliparous obese women remained at elevated risk for spontaneous and indicated extremely preterm delivery (Table S1). However, the risks of indicated very preterm delivery were attenuated and no longer significant. Similarly, multiparous obese women remained at decreased risk for spontaneous moderate to late preterm delivery, but the increased risks of indicated delivery at moderate to late preterm were attenuated among both nulliparous and multiparous women.

For all women in the cohort including non-obese, as the gestational age at delivery increased, the percentage of spontaneous precursors (spontaneous labor and PPROM) decreased and the proportion of no indication including elective delivery increased (Table 3). Among indicated precursors, pregnancy related hypertensive disorders including gestational hypertension, preeclampsia or eclampsia was the most common condition for all gestational age categories at preterm delivery among both parity groups except for extremely preterm delivery among multiparous women where fetal anomaly was the most common precursor. The percentage of maternal conditions increased as the gestational age at preterm delivery increased.

As presented in Figure 1, the composition of preterm precursors differed by prepregnancy obesity status for the gestational age. A distinct trend was not observed among extremely preterm deliveries however preeclampsia/eclampsia increased by prepregnancy BMI among nulliparous women. Among very preterm deliveries, spontaneous labor decreased, whereas preeclampsia/eclampsia increased with the increase of prepregnancy BMI among multiparous women. The increased proportion of indicated precursors and the decreased proportion of spontaneous labor with the increase of prepregnancy BMI were more pronounced among moderate to late preterm deliveries for both nulliparous and multiparous women. Preeclampsia/eclampsia accounted for a higher proportion in precursors of preterm delivery among nulliparous women compared with multiparous women at the same gestational age at delivery and obesity subgroup.

## Discussion

### Main findings

Among women without chronic disease, maternal obesity was associated with preterm delivery and those risks differed by gestational age at delivery, preterm category, and parity. Maternal obesity increased the risks of both spontaneous and indicated extremely preterm

delivery among nulliparous women. For moderate to late preterm delivery, maternal BMI was inversely associated with spontaneous preterm delivery among multiparous women, but the risk of indicated preterm delivery increased significantly regardless of parity. Much of the increased risk of indicated moderate to late preterm delivery were attenuated when excluding the subsequent development of pregnancy complications including gestational hypertensive disorders and gestational diabetes. The risks of extremely preterm delivery, both spontaneous and indicated, remained elevated among nulliparous obese women who did not develop these complications, however, some of the pregnancy complications might have developed later in gestation for some of those pregnancies.

### Strengths and limitations

The major advantage of our study was the large obstetric cohort with detailed clinical data that allowed us to comprehensively exclude chronic diseases and to classify indicated versus spontaneous preterm delivery. The large sample size also enabled us to study obesity severity. A limitation of our study is that prepregnancy BMI was not available for 33.5% of singleton deliveries, likely because the information was not entered into the electronic medical records upon admission to labor and delivery. It is reassuring to note that in instances where the missing predictor variable is unrelated to the outcome, a complete case analysis will not be biased.<sup>20</sup> The precursors of indicated preterm delivery were derived from the indications for induction and cesarean delivery. For cases in which the information was not provided, we used medical, obstetric, or fetal conditions in an effort to capture the potential reasons for delivery. However, since we categorized preterm deliveries in a hierarchical manner, it is not likely that the incidence of indicated preterm delivery was overestimated.

### Interpretation

Prior studies did not comprehensively exclude women with pre-gravid chronic diseases,<sup>11, 21–31</sup> even though some considered several maternal prepregnancy conditions in the risk assessment model<sup>26, 28–30</sup> or sensitivity analysis,<sup>21, 22, 25</sup> and fewer studied both categories (spontaneous, indicated/induced) of preterm delivery by gestational timing,<sup>21–23, 26</sup> classified obesity by class<sup>11, 21, 23, 29</sup> or stratified by parity.<sup>11, 12, 31</sup> Among studies which reported overall risk of spontaneous preterm deliveries in association with prepregnancy obesity, some reported null associations,<sup>30</sup> or an increased overall risk among obese women,<sup>21, 23</sup> whereas others reported a decreased risk.<sup>11, 25, 29</sup> Difference in preterm delivery incidence, case classification, racial composition, and study design could partly explain these inconsistencies. Moreover, based on our findings, relative composition of parity, categories of preterm delivery, and preterm precursors of the study populations might have influenced the conflicting results.

Our finding of increased risk of spontaneous preterm delivery at 23–27 weeks among obese nulliparous women is similar to a previous large California study,<sup>31</sup> based on birth records linked with hospital discharge data that excluded chronic as well as gestational hypertension and diabetes and stratified by parity, and another Swedish study<sup>21</sup> based on birth registry that included women with chronic diseases. Shaw et al.<sup>31</sup> also reported an inverse



association between excess prepregnancy BMI and the risk of spontaneous moderate to late preterm delivery which is similar to our results.

The overall association between the risk of indicated/induced preterm delivery and prepregnancy obesity were positive in most of previous literature.<sup>11, 21, 22, 26, 29, 30</sup> We provided novel findings on indicated preterm deliveries stratified by gestational age categories and parity. Several studies<sup>21, 22, 26</sup> considered gestational age at preterm delivery but did not separate nulliparous and multiparous women. We found the risk of indicated extremely preterm delivery varied by parity, i.e. overweight and obese nulliparous women were at increased risk up to 2.5 fold whereas no association was observed among multiparous women. The attenuated associations in the sensitivity analysis restricted to women who did not develop pregnancy complications suggest that pregnancy complications might largely influence the associations between maternal obesity and indicated preterm delivery, although nulliparous obese women still had an increased risk of indicated extremely preterm delivery. Cnattingius et al.<sup>21</sup> also observed a reduction or elimination of increased risks of indicated preterm delivery in their sensitivity analysis among obese women without pre- and gestational hypertensive disorders and diabetes. The large sample size enabled us to study specific classifications of preterm delivery; however, caution is needed to interpret the results since the number of cases of lower gestational age is still small.

The biological mechanisms between overweight and obesity and preterm delivery are likely to be complex. Intrauterine infection and maternal and fetal inflammation are proposed to be in the pathological pathway leading to preterm labor and PPRM.<sup>32</sup> Chorioamnionitis is reported to be associated with premature rupture of membrane and preterm delivery,<sup>33</sup> and more common among obese pregnant women.<sup>34</sup> Elevated levels of maternal systemic inflammation markers, including plasma or serum interleukin-6<sup>35, 36</sup> and interferon- $\gamma$ <sup>36</sup> appear to increase the odds of spontaneous preterm delivery and obese pregnant women without known diseases have elevated plasma C-reactive protein and interleukin-6 concentrations.<sup>37</sup> Furthermore, increased level of C-reactive protein and dyslipidemia early in pregnancy were associated with increased risk of spontaneous preterm delivery.<sup>38</sup> These potential inflammatory pathways can lead to spontaneous preterm delivery through the maternal metabolic syndrome<sup>39</sup> and increased systematic inflammation<sup>40</sup> reported among obese pregnant women without chronic diseases.

On the other hand, prior studies have shown that shorter cervix length was associated with increased risk of preterm delivery.<sup>41</sup> Mid-trimester cervix length was positively associated with prepregnancy BMI and shorter among nulliparous women compared with multiparous women.<sup>42</sup> Hendler et al.<sup>25</sup> proposed that a longer cervix length in obese women could explain the reduced risk of spontaneous preterm delivery. Taken together, these data correspond to our finding of decreased risk of spontaneous late preterm delivery among multiparous overweight and obese women. Decreased risk of spontaneous late preterm delivery also should be considered in relation to the concurrent increase of indicated preterm delivery by the severity of maternal obesity. Women who develop pregnancy complications might be delivered before the onset of spontaneous labor or PPRM which could lower the rate of spontaneous labor and PPRM among obese women at the later gestational age.<sup>43</sup>

However, the decreased risk of spontaneous preterm delivery between 32–36 weeks of gestation was not attenuated but more pronounced after we excluded women with pregnancy complications among multiparous women. These findings suggest that factors along the pathway of spontaneous labor and PPRM could differ by gestational period and interact differently according to the degree of maternal obesity.

## Conclusion

Higher prepregnancy BMI was associated with increased risk of preterm delivery in the absence of chronic diseases. We provide strong evidence that maternal weight influences indicated preterm delivery outside of the underlying chronic conditions that tend to co-occur with obesity. Furthermore, by examining gestational age at delivery in detail, we were able to provide a more comprehensive overview of variations in risk for both spontaneous and indicated preterm delivery.

Optimizing maternal weight prior to pregnancy as a measure of primary prevention to reduce preterm delivery merits further study among overweight and obese women without chronic disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*. 2008; 371(9608):261–9. [PubMed: 18207020]
2. MacDorman MF, Matthews TJ, Mohangoo AD, Zeitlin J. International comparisons of infant mortality and related factors: United States and Europe, 2010. *Natl Vital Stat Rep*. 2014; 63(5):1–6.
3. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. *N Engl J Med*. 2015; 372(4):331–40. [PubMed: 25607427]
4. Matthews TJ, MacDorman MF. Infant mortality statistics from the 2010 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2013; 62(8):1–26.
5. Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. *Obstet Gynecol*. 2011; 118(2 Pt 1):305–12. [PubMed: 21775846]



6. McIntyre HD, Gibbons KS, Flenady VJ, Callaway LK. Overweight and obesity in Australian mothers: epidemic or endemic? *Med J Aust.* 2012; 196(3):184–8. [PubMed: 22339524]
7. Mbah AK, Kornosky JL, Kristensen S, August EM, Alio AP, Marty PJ, et al. Super-obesity and risk for early and late pre-eclampsia. *BJOG.* 2010; 117(8):997–1004. [PubMed: 20482533]
8. Baeten JM, Bukusi EA, Lambe M. Pregnancy complications and outcomes among overweight and obese nulliparous women. *Am J Public Health.* 2001; 91(3):436–40. [PubMed: 11236410]
9. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA.* 2009; 301(6):636–50. [PubMed: 19211471]
10. Torloni MR, Betran AP, Daher S, Widmer M, Dolan SM, Menon R, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. *J Matern Fetal Neonatal Med.* 2009; 22(11):957–70. [PubMed: 19900068]
11. Smith GC, Shah I, Pell JP, Crossley JA, Dobbie R. Maternal obesity in early pregnancy and risk of spontaneous and elective preterm deliveries: a retrospective cohort study. *Am J Public Health.* 2007; 97(1):157–62. [PubMed: 17138924]
12. Salihu H, Mbah AK, Alio AP, Kornosky JL, Whiteman VE, Belogolovkin V, et al. Nulliparity and preterm birth in the era of obesity epidemic. *J Matern Fetal Neonatal Med.* 2010; 23(12):1444–50. [PubMed: 20482286]
13. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ.* 2014; 348:g2301. [PubMed: 24735917]
14. Kendrick J, Sharma S, Holmen J, Palit S, Nuccio E, Chonchol M. Kidney Disease and Maternal and Fetal Outcomes in Pregnancy. *Am J Kidney Dis.* 2015; 66(1):55–9. [PubMed: 25600490]
15. Tucker CM, Berrien K, Menard MK, Herring AH, Daniels J, Rowley DL, et al. Predicting Preterm Birth Among Women Screened by North Carolina's Pregnancy Medical Home Program. *Matern Child Health J.* 2015
16. Zhang J, Troendle J, Reddy UM, Laughon SK, Branch DW, Burkman R, et al. Contemporary cesarean delivery practice in the United States. *Am J Obstet Gynecol.* 2010; 203(4):326 e1–e10. [PubMed: 20708166]
17. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet.* 2012; 379(9832):2162–72. [PubMed: 22682464]
18. Laughon SK, Reddy UM, Sun L, Zhang J. Precursors for late preterm birth in singleton gestations. *Obstet Gynecol.* 2010; 116(5):1047–55. [PubMed: 20966688]
19. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res.* 2013; 22(6):661–70. [PubMed: 22072596]
20. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj.* 2009; 338:b2393. [PubMed: 19564179]
21. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, et al. Maternal obesity and risk of preterm delivery. *JAMA.* 2013; 309(22):2362–70. [PubMed: 23757084]
22. Nohr EA, Bech BH, Vaeth M, Rasmussen KM, Henriksen TB, Olsen J. Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort. *Paediatr Perinat Epidemiol.* 2007; 21(1):5–14. [PubMed: 17239174]
23. Khatibi A, Brantsaeter AL, Sengpiel V, Kacerovsky M, Magnus P, Morken NH, et al. Prepregnancy maternal body mass index and preterm delivery. *Am J Obstet Gynecol.* 2012; 207(3):212 e1–7. [PubMed: 22835494]
24. Raisanen S, Gissler M, Saari J, Kramer M, Heinonen S. Contribution of risk factors to extremely, very and moderately preterm births - register-based analysis of 1,390,742 singleton births. *PLoS One.* 2013; 8(4):e60660. [PubMed: 23577142]

25. Hendler I, Goldenberg RL, Mercer BM, Iams JD, Meis PJ, Moawad AH, et al. The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. *Am J Obstet Gynecol*. 2005; 192(3):882–6. [PubMed: 15746686]
26. Parker MG, Ouyang F, Pearson C, Gillman MW, Belfort MB, Hong X, et al. Prepregnancy body mass index and risk of preterm birth: association heterogeneity by preterm subgroups. *BMC Pregnancy Childbirth*. 2014; 14:153. [PubMed: 24779674]
27. Masho SW, Bishop DL, Munn M. Pre-pregnancy BMI and weight gain: where is the tipping point for preterm birth? *BMC Pregnancy Childbirth*. 2013; 13:120. [PubMed: 23706121]
28. Zhong Y, Cahill AG, Macones GA, Zhu F, Odibo AO. The association between prepregnancy maternal body mass index and preterm delivery. *Am J Perinatol*. 2010; 27(4):293–8. [PubMed: 19823961]
29. Salihu HM, Lynch O, Alio AP, Liu J. Obesity subtypes and risk of spontaneous versus medically indicated preterm births in singletons and twins. *Am J Epidemiol*. 2008; 168(1):13–20. [PubMed: 18456643]
30. Rudra CB, Frederick IO, Williams MA. Pre-pregnancy body mass index and weight gain during pregnancy in relation to preterm delivery subtypes. *Acta Obstet Gynecol Scand*. 2008; 87(5):510–7. [PubMed: 18446533]
31. Shaw GM, Wise PH, Mayo J, Carmichael SL, Ley C, Lyell DJ, et al. Maternal prepregnancy body mass index and risk of spontaneous preterm birth. *Paediatr Perinat Epidemiol*. 2014; 28(4):302–11. [PubMed: 24810721]
32. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. *BJOG*. 2006; 113(Suppl 3):17–42.
33. Mueller-Heubach E, Rubinstein DN, Schwarz SS. Histologic chorioamnionitis and preterm delivery in different patient populations. *Obstet Gynecol*. 1990; 75(4):622–6. [PubMed: 2314782]
34. Raatikainen K, Heiskanen N, Heinonen S. Transition from overweight to obesity worsens pregnancy outcome in a BMI-dependent manner. *Obesity*. 2006; 14(1):165–71. [PubMed: 16493135]
35. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. *Am J Reprod Immunol*. 2014; 72(3):326–36. [PubMed: 24807462]
36. Curry AE, Vogel I, Drews C, Schendel D, Skogstrand K, Flanders WD, et al. Mid-pregnancy maternal plasma levels of interleukin 2, 6, and 12, tumor necrosis factor-alpha, interferon-gamma, and granulocyte-macrophage colony-stimulating factor and spontaneous preterm delivery. *Acta Obstet Gynecol Scand*. 2007; 86(9):1103–10. [PubMed: 17712652]
37. Ramsay JE, Ferrell WR, Crawford L, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J Clin Endocrinol Metab*. 2002; 87(9):4231–7. [PubMed: 12213876]
38. Catov JM, Bodnar LM, Ness RB, Barron SJ, Roberts JM. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. *Am J Epidemiol*. 2007; 166(11):1312–9. [PubMed: 17906337]
39. Gargano JW, Holzman C, Senagore P, Thorsen P, Skogstrand K, Hougaard DM, et al. Mid-pregnancy circulating cytokine levels, histologic chorioamnionitis and spontaneous preterm birth. *J Reprod Immunol*. 2008; 79(1):100–10. [PubMed: 18814919]
40. Stewart FM, Freeman DJ, Ramsay JE, Greer IA, Caslake M, Ferrell WR. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. *J Clin Endocrinol Metab*. 2007; 92(3):969–75. [PubMed: 17192290]
41. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. *N Engl J Med*. 1996; 334(9):567–72. [PubMed: 8569824]
42. van der Ven AJ, van Os MA, Kleinrouweler CE, de Groot CJ, Haak MC, Mol BW, et al. Is cervical length associated with maternal characteristics? *Eur J Obstet Gynecol Reprod Biol*. 2015; 188:12–6. [PubMed: 25770842]

43. Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol.* 2011; 118(2 Pt 1):323–33. [PubMed: 21775849]

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**Tweetable abstract**

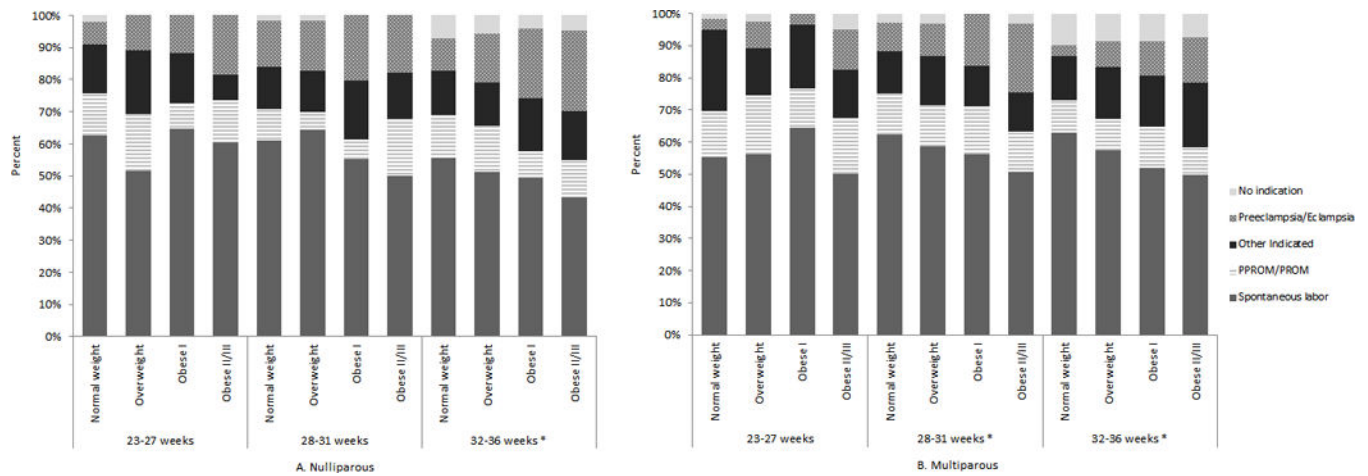
Obese nulliparas without chronic disease had higher risk for spontaneous delivery < 28 weeks'

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**Figure 1.**

Precursors for preterm delivery among women without prepregnancy chronic diseases by prepregnancy obesity, gestational weeks at delivery and parity, Consortium on Safe Labor 2002–2008. A. Nulliparous women; B. Multiparous women

**Table 1**

Demographic characteristics of singleton pregnancies among women without pre-pregnancy chronic diseases by gestational weeks at delivery, Consortium on Safe Labor 2002–2008

Characteristics	Extremely preterm (23–27 weeks)	Very preterm (28–31 weeks)	Moderate to late preterm (32–36 weeks)	Term (≥ 37 weeks)	P value <sup>a</sup>
n (%)	753 (0.7)	1021 (1.0)	8164 (7.7)	96391 (90.7)	
Age (years), mean (±SD)	27.6 (±6.0)	27.3 (±6.7)	27.1 (±6.5)	27.4 (±6.3)	< 0.001
Body mass index <sup>a</sup>					< 0.001
Normal	367 (48.7)	540 (52.9)	4726 (57.9)	57731 (60.0)	
Overweight	201 (26.7)	259 (25.4)	1914 (23.4)	22472 (23.3)	
Obese I	107 (14.2)	129 (12.6)	897 (11.0)	9706 (10.1)	
Obese II/III	78 (10.4)	93 (9.1)	627 (7.7)	6482 (6.7)	
Race/ethnicity, n (%)					< 0.001
White	204 (27.1)	372 (36.4)	3667 (44.9)	50342 (52.2)	
Black	286 (38.0)	316 (31.0)	2058 (25.2)	16855 (17.5)	
Hispanic	174 (23.1)	229 (22.4)	1709 (20.9)	19706 (20.4)	
Others/unknown	89 (11.8)	104 (10.2)	730 (9.0)	9488 (9.8)	
Marital status, n (%)					< 0.001
Married	340 (45.2)	486 (47.6)	4651 (57.0)	64054 (66.5)	
Unmarried/unknown	413 (54.9)	536 (52.4)	3513 (43.1)	32337 (33.6)	
Insurance type, n (%)					< 0.001
Private	295 (39.2)	431 (42.2)	3876 (47.5)	53286 (55.3)	
Public/self pay	339 (45.0)	436 (42.7)	2949 (36.1)	27754 (28.8)	
Others/unknown	119 (15.8)	154 (15.1)	1339 (16.4)	15351 (15.9)	
Parity, n (%)					0.005
Nulliparous	370 (49.1)	460 (45.1)	3346 (41.0)	39024 (40.5)	
Smoking during pregnancy, n (%)	62 (8.2)	97 (9.5)	599 (7.3)	4534 (4.7)	< 0.001
Alcohol use during pregnancy, n (%)	20 (2.7)	30 (2.9)	143 (1.8)	1439 (1.5)	< 0.001

<sup>a</sup>Normal (18.5–24.9 kg/m<sup>2</sup>); overweight (25–29.9); class I (30–34.9); class II/III obese (≥ 35)

<sup>b</sup>P values were based on generalized estimating equations that account for multiple pregnancies to same women.



Risks of spontaneous and indicated preterm delivery in singleton pregnancies among women without pre-pregnancy chronic diseases by pre-pregnancy obesity, gestational weeks at delivery and parity, Consortium on Safe Labor 2002–2008

**Table 2**

Outcomes	Normal BMI (18.5–24.9)		Overweight (25–29.9)		Obese I (30–34.9)		Obese II/III (≥ 35)		P for trend <sup>b</sup>
	N (%)	RR	N (%)	RR (95% CI) <sup>a</sup>	N (%)	RR (95% CI) <sup>a</sup>	N (%)	RR (95% CI) <sup>a</sup>	
Nulliparous (n=43,200)									
Extremely preterm									
Spontaneous <sup>c</sup>	144(0.5)	Reference	63 (0.7)	1.26 (0.94, 1.70)	37 (1.1)	1.88 (1.30, 2.71)	28 (1.3)	1.99 (1.32, 3.01)	< 0.001
Indicated	42 (0.2)	Reference	28 (0.3)	1.94 (1.19, 3.15)	14 (0.4)	2.49 (1.34, 4.62)	10 (0.4)	2.46 (1.21, 5.00)	< 0.001
Very preterm <sup>d</sup>									
Spontaneous <sup>c</sup>	194 (0.7)	Reference	76 (0.9)	1.16 (0.89, 1.51)	30 (0.9)	1.16(0.79, 1.72)	19 (0.9)	1.05 (0.65, 1.70)	0.46
Indicated	75 (0.3)	Reference	31 (0.4)	1.15 (0.76, 1.76)	19 (0.6)	1.70 (1.02, 2.81)	9 (0.4)	1.12 (0.56, 2.26)	0.20
Moderate to late preterm <sup>e</sup>									
Spontaneous <sup>c</sup>	1,474 (5.2)	Reference	458 (5.2)	0.96 (0.86, 1.06)	174 (5.3)	0.95 (0.81, 1.11)	114 (5.3)	0.92 (0.76, 1.11)	0.25
Indicated	513 (1.8)	Reference	202 (2.3)	1.20 (1.02, 1.41)	114 (3.5)	1.75 (1.42, 2.15)	84 (3.9)	1.89 (1.49, 2.39)	< 0.001
Multiparous (n=63,129)									
Extremely preterm									
Spontaneous <sup>c</sup>	123 (0.4)	Reference	82 (0.5)	1.16 (0.88, 1.54)	43 (0.6)	1.19 (0.84, 1.71)	27 (0.5)	0.99 (0.64, 1.52)	0.68
Indicated	51 (0.2)	Reference	25 (0.2)	0.89 (0.55, 1.45)	13 (0.2)	0.81 (0.45, 1.47)	11 (0.2)	0.99 (0.52, 1.89)	0.75
Very preterm <sup>d</sup>									
Spontaneous <sup>c</sup>	200 (0.6)	Reference	107 (0.7)	1.05 (0.83, 1.33)	57 (0.8)	1.13 (0.84, 1.52)	41 (0.8)	1.13 (0.79, 1.61)	0.36
Indicated	58 (0.2)	Reference	38 (0.2)	1.19 (0.79, 1.78)	23 (0.3)	1.39 (0.85, 2.27)	22 (0.4)	1.82 (1.10, 3.00)	0.02
Moderate to late preterm <sup>e</sup>									
Spontaneous <sup>c</sup>	1,889 (5.5)	Reference	817 (5.2)	0.90 (0.83, 0.97)	386 (5.3)	0.87 (0.78, 0.97)	245 (5.0)	0.79 (0.69, 0.90)	< 0.001
Indicated	445 (1.3)	Reference	291 (1.9)	1.26 (1.08, 1.46)	158 (2.2)	1.37 (1.13, 1.65)	142 (2.9)	1.69 (1.39, 2.05)	< 0.001

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$\beta$  Adjusted for site, maternal age, race/ethnicity, insurance type, marital status, parity and smoking and alcohol consumption during pregnancy.  
 $\gamma$  Test of linear trend were conducted by using the median value for each obesity group and fitting this as a continuous variable in the regression models.  
 $\zeta$  Spontaneous preterm births included spontaneous labor and PPROM  
 $d$  Preterm delivery before 28 weeks of gestation was excluded in the denominator for rate calculation and analysis.  
 $e$  Preterm delivery before 32 weeks of gestation was excluded in the denominator for rate calculation and analysis.

Precursors for preterm delivery among women without pre-pregnancy chronic diseases by gestational weeks at delivery and parity

Table 3

	Nulliparous				Multiparous			
	Extremely preterm (n=370) %	Very preterm (n=460) %	Moderate to late preterm (n=3,346) %	Term (n=39,024) %	Extremely preterm (n=383) %	Very preterm (n=561) %	Moderate to late preterm (n=4,818) %	Term (n=57,367) %
Precursors <sup>a</sup>								
Spontaneous labor	60.0	60.4	53.4	50.9	56.4	59.2	59.1	54.0
PPROM/PPROM	13.5	8.9	13.0	5.5	15.4	15.4	10.2	2.6
Indicated	25.4	29.1	27.3	19.3	26.1	26.1	21.5	14.6
No indication	1.1	1.5	6.4	24.3	2.1	2.1	9.2	28.9
Specific indications <sup>b</sup>								
Chorioamnionitis	3.2	3.0	1.5	2.9	2.0	1.4	0.7	0.7
Decidual hemorrhage or abruption	10.6	8.2	5.3	2.7	5.0	15.6	8.7	4.4
Placenta previa	3.2	3.0	4.1	1.2	10.0	16.3	7.1	1.4
Gestational hypertensive disease	41.5	55.2	56.9	31.1	23.0	46.8	37.0	16.4
Gestational hypertension	3.2	2.2	8.3	14.4	1.0	0.7	7.5	8.1
Preeclampsia/Eclampsia	38.3	53.0	48.5	16.7	22.0	46.1	29.4	8.3
Maternal condition <sup>c</sup>	9.6	12.7	19.4	22.1	7.0	12.8	23.4	28.4
Gestational Diabetes	7.5	6.0	10.6	11.9	2.0	9.2	14.6	18.9
Fetal anomaly	37.2	30.6	15.0	14.4	35.0	27.7	12.8	17.4
Antepartum stillbirth	21.3	14.2	2.5	0.3	27.0	10.6	2.4	0.4
Suspected fetal macrosomia	0.0	0.8	0.6	5.9	0.0	0.0	1.4	5.7
Fetal condition <sup>d</sup>	25.5	39.6	33.7	38.7	28.0	26.2	33.6	25.8
Maternal fever on admission	2.1	3.7	1.2	1.2	1.0	4.3	1.0	0.9
Admission for maternal reason, not specified <sup>e</sup>	4.3	5.2	2.7	1.2	7.0	2.1	3.4	1.1
Admission for fetal reason, not specified <sup>e</sup>	2.1	0.0	0.7	1.1	0.0	0.0	0.4	1.7

	Nulliparous				Multiparous			
	Extremely preterm (n=370) %	Very preterm (n=460) %	Moderate to late preterm (n=3,346) %	Term (n=39,024) %	Extremely preterm (n=383) %	Very preterm (n=561) %	Moderate to late preterm (n=4,818) %	Term (n=57,367) %
History of maternal or obstetric condition <sup>f</sup>	–	–	–	–	0.0	0.0	0.3	0.6
History of fetal condition <sup>f</sup>	–	–	–	–	13.0	9.9	10.9	19.3

<sup>a</sup> Both p values for significance testing for percentages of precursors (spontaneous labor, PPRM/PPROM, indicated, others/no recorded indication) among gestational weeks of delivery of nulliparous and multiparous women were < 0.001.

<sup>b</sup> Specific categories for the “indicated” precursors can add up to more than 100% because women could have more than one pregnancy condition.

<sup>c</sup> Maternal conditions included gestational diabetes, polyhydramnios, thromboembolic disorder, active genital herpes, and other maternal indication for induction.

<sup>d</sup> Fetal conditions included intrauterine growth restriction, abnormal antenatal testing, oligohydramnios, Rh incompatibility and other fetal indication for induction.

<sup>e</sup> Admission for maternal or obstetric or fetal reasons included only if there was no other pregnancy condition. These two categories are exclusive of other indications.

<sup>f</sup> History of maternal or obstetric and fetal conditions included pregnancy complications in previous pregnancy such as history of fetal demise or traumatic first delivery.