Maternal Obesity and Risk of Preterm Delivery

Sven Cnattingius, MD, PhD
Eduardo Villamor, MD, DrPH
Stefan Johansson, MD, PhD
Anna-Karin Edstedt Bonamy, MD, PhD
Martina Persson, MD, PhD
Anna-Karin Wikström, MD, PhD
Fredrik Granath, PhD

Importance Preterm birth is a leading cause of infant mortality, morbidity, and long-term disability, and these risks increase with decreasing gestational age. Obesity increases the risk of preterm delivery, but the associations between overweight and obesity and subtypes of preterm delivery are not clear.

Objective To study the associations between early pregnancy body mass index (BMI) and risk of preterm delivery by gestational age and by precursors of preterm delivery.

Design, Setting, and Participants Population-based cohort study of women with live singleton births in Sweden from 1992 through 2010. Maternal and pregnancy characteristics were obtained from the nationwide Swedish Medical Birth Register.

Main Outcomes and Measures Risks of preterm deliveries (extremely, 22-27 weeks; very, 28-31 weeks; and moderately, 32-36 weeks). These outcomes were further characterized as spontaneous (related to preterm contractions or preterm premature rupture of membranes) and medically indicated preterm delivery (cesarean delivery before onset of labor or induced onset of labor). Risk estimates were adjusted for maternal age, parity, smoking, education, height, mother's country of birth, and year of delivery.

Results Among 1 599 551 deliveries with information on early pregnancy BMI, 3082 were extremely preterm, 6893 were very preterm, and 67 059 were moderately preterm. Risks of extremely, very, and moderately preterm deliveries increased with BMI and the overweight and obesity-related risks were highest for extremely preterm delivery. Among normal-weight women (BMI 18.5-<25), the rate of extremely preterm delivery was 0.17%. As compared with normal-weight women, rates (%) and adjusted odds ratios (ORs [95% CIs]) of extremely preterm delivery were as follows: BMI 25 to less than 30 (0.21%; OR, 1.26; 95% CI, 1.15-1.37), BMI 30 to less than 35 (0.27%; OR, 1.58; 95% CI, 1.39-1.79), BMI 35 to less than 40 (0.35%; OR, 2.01; 95% CI, 1.66-2.45), and BMI of 40 or greater (0.52%; OR, 2.99; 95% CI, 2.28-3.92). Risk of spontaneous extremely preterm delivery increased with BMI among obese women (BMI≥30). Risks of medically indicated preterm deliveries increased with BMI among overweight and obese women.

Conclusions and Relevance In Sweden, maternal overweight and obesity during pregnancy were associated with increased risks of preterm delivery, especially extremely preterm delivery. These associations should be assessed in other populations.

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Maternal overweight and obesity has, due to the high prevalence and associated risks, replaced smoking as the most important preventable risk factor for adverse pregnancy outcomes in many countries.[1]

Preterm birth, defined as a delivery of a liveborn infant before 37 gestational weeks, is the leading cause of infant mortality, neonatal morbidity, and long-term disability among nonmalformed infants,[2] and these risks increase with decreasing gestational age.[3] Two reviews reported that women with obesity grades 2 to 3 (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] ≥35) have increased risks of very and moderately preterm delivery (<32 weeks and 32-36 weeks, respectively),[4,5] while associations between overweight (BMI 25-<30) and obesity grade 1 (BMI 30-<35) and preterm delivery are less consistent.[5-7] Two studies have also recently reported an increased risk of extremely preterm delivery (< 28 weeks) among obese (BMI≥30) women.[8,9]

Obesity increases the risk of medically indicated preterm delivery,[4,5] partly or substantially through obesity-related maternal disorders including preeclampsia.[6,7] Whether obesity influences the risk of spontaneous preterm delivery is less clear,[4,5] and a potential association may differ by length of gestation. For example, obesity could be related to infection and inflammation, which is more associated with extremely preterm delivery than with the moderately preterm subset.[10,11]

Between 1992 and 2010, the nationwide Swedish Medical Birth Register included information on early preg-

Author Affiliations: Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska University Hospital (Drs Cnattingius, Johansson, Edstedt Bonamy, Persson, Wikström, and Granath), and Department of Clinical Science, Intervention, and Technology (Dr Persson), Karolinska Institutet, Stockholm, Sweden; Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor (Dr Villamor); and Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden (Dr Wikström).
Corresponding Author: Sven Cnattingius, MD, PhD, Clinical Epidemiology Unit, T2, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, SE-171 76 Stockholm, Sweden (sven.cnattingius@ki.se).

nancy BMI and gestational age for more than 1.5 million deliveries. Using this data set, we were able to disentangle risks of preterm delivery by gestation and by spontaneous and medically indicated preterm deliveries among women with overweight and different grades of obesity.

METHODS

Study Population

The Swedish Medical Birth Register includes information on more than 98% of births in Sweden from 1973 forward.[12] Information on live births is included from 22 completed weeks and information on stillbirths is included from 28 completed weeks (1973 through 2007) or from 22 completed weeks (2008 forward). We included pregnancies with live singleton births, as multiple pregnancies are at a substantially increased risk of preterm delivery and preterm birth may be a consequence of stillbirth. Because information on maternal height and weight is included from 1992 forward, we restricted our study period to 1992 through 2010.

The Swedish Medical Birth Register includes prospectively collected information from standardized prenatal, obstetric, and neonatal records available at all prenatal clinics and hospitals, and copies of these forms are forwarded to the Birth Register after delivery. The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

In Sweden, the general policy is that women undergo a first prenatal visit at 8 to 12 gestational weeks.[12] Maternal height and smoking status are self-reported and maternal weight is measured in light indoor clothing. Eight to 10 visits are recommended in low-risk pregnancies. Blood pressure, proteinuria, and glucosuria are checked throughout the course of visits and all women are screened for gestational diabetes (predominantly by using capillary glucose, measured 4-6 times during pregnancy starting with the first prenatal visit). Information about maternal age and parity is collected at delivery. Information about gestational length at first prenatal visit was available from 1996 forward (using information on dates at first prenatal visit and delivery and gestational age at delivery). Using the person-unique national registration numbers, information about each mother's country of birth and level of education was achieved by cross-linking the Swedish Medical Birth Register to the nationwide Swedish Population and Education Registers.

BMI was calculated from information on height and weight at the first prenatal visit. BMI was used to characterize the women as underweight (BMI<18.5), normal (18.5-<25), overweight (25-<30), obese grade 1 (30-<35), obese grade 2 (35-<40), or obese grade 3 (≥40).[13]

Information about maternal diseases or pregnancy complications was classified by the woman's physician at the time of hospital discharge according to the Swedish version of the International Classification of Diseases, Ninth and Tenth Revisions (*ICD-9* and *ICD-10*, respectively). Information about obesity-related maternal disorders included pregestational hypertension (self-reported by checking a box at the first prenatal visit or by *ICD-9* codes 401-405, 642C, and 642H, and *ICD-10* codes I10-I15, O10, and O11), pregestational diabetes (insulin-dependent or noninsulin-dependent, *ICD-9* codes 250 and 648A and *ICD-10* codes E10-E14 and O240-O243), preeclampsia (including eclampsia, *ICD-9* codes 642E-642G and *ICD-10* codes O14 and O15), and gestational diabetes (*ICD-9* code 648W and *ICD-10* code O244).

Gestational age was determined using the following hierarchy: early second trimester ultrasound (1 506 897 [81.1%]), date of last menstrual period reported at the first prenatal visit (244 638 [13.2%]), and from a postnatal assessment (106 287 [5.7%]). In Sweden, an ultrasonic scan, generally performed in the 18th week of gestation or earlier, is offered to all pregnant women and accepted by 95%.[14] Information on expected date of delivery, both by ultrasound and by date of last menstrual period, was available in 76.2% (1 416 413) of all deliveries.

Definition of Outcome

Delivery was categorized as extremely, very, and moderately preterm (22-27, 28-31, and 32-36 completed weeks, respectively).[15] Based on information from checked boxes recorded in the obstetrical record before delivery, preterm deliveries were further stratified as either spontaneous or medically indicated, the latter defined as performance of a cesarean delivery before onset of labor or induction of labor. Spontaneous preterm deliveries were stratified into preterm premature rupture of the membranes (*ICD-9* code 658B and *ICD-10* code O42) or preterm labor.

Statistical Analysis

Rates of extremely preterm deliveries (by percent) were calculated as the proportion of all deliveries that were extremely preterm. When calculating rates of very (28-31 weeks) and moderately (32-36 weeks) preterm deliveries, deliveries before 28 weeks and before 32 weeks were excluded in the denominators, respectively. Logistic regression analysis was used to estimate the associations between BMI in early pregnancy and risks of preterm delivery. In all analyses, odds ratios (ORs) with 95% CIs were calculated using the generalized estimating equation method because observations were not independent in women who delivered more than once during the study period. Predictors included BMI categories and potential confounders (maternal age, parity, cigarette smoking, education, maternal height, mother's country of birth, and year of delivery). Variables were categorized as in TABLE 1 and TABLE 2.

We calculated ORs and 95% CIs for deliveries in the extremely, very, and moderately preterm categories. The adjusted absolute risks attributable to different BMI categories were estimated as $p_0 \times (OR-1)$, in which p_0 is the crude absolute risk among mothers with normal BMI. We also investigated potential differences in risks by methods used to estimate gestational age and BMI-related risks of preterm delivery in a subsample in whom BMI was recorded in the first trimester (ie, within 14 completed gestational weeks).

Next, we estimated ORs and 95% CIs of extremely, very, and moderately spontaneous preterm deliveries (including separate analyses for preterm delivery due to premature rupture of the membranes and spontaneous labor) and medically indicated preterm deliveries. Finally, we estimated risks of preterm delivery after excluding pregnancies with obesity-related maternal diseases (ie, pregestational hypertension, preeclampsia, and pregestational and gestational diabetes).

Table 1. Maternal Clinical Characteristics and Rates of Preterm Singleton Deliveries in Sweden 1992-2010

	No. of Women (n = 1 857 822)[a]	Weeks Gestation, No. (%) 22-27 (n = 4250)[b]	28-31 (n = 8638)[b]	32-36 (n = 80 531)[b]
Body mass index				
<18.5	41 486	85 (0.20)	216 (0.52)	2382 (5.78)
18.5-<25	1 014 513	1703 (0.17)	4001 (0.40)	40 766 (4.04)
25-<30	385 599	818 (0.21)	1695 (0.44)	16 143 (4.21)
30-<35	114 421	306 (0.27)	648 (0.57)	5380 (4.74)
35-<40	32 677	114 (0.35)	232 (0.71)	1743 (5.39)
≥40	10 855	56 (0.52)	101 (0.94)	645 (6.03)
Data missing	258 271	1168 (0.45)	1745 (0.68)	13 472 (5.28)
Height, cm				
<155	54 637	171 (0.31)	374 (0.69)	3496 (6.46)
155-164	607 971	1331 (0.22)	2902 (0.48)	28 778 (4.77)
165-174	891 337	1563 (0.18)	3627 (0.41)	34 649 (3.91)
≥175	163 870	251 (0.15)	525 (0.32)	5323 (3.26)
Data missing	140 007	934 (0.67)	1210 (0.87)	8285 (6.01)
Parity				
1	802 870	2273 (0.28)	4722 (0.59)	42 434 (5.33)
2-3	939 284	1607 (0.17)	3299 (0.35)	32 213 (3.45)
≥4	115 668	370 (0.32)	617 (0.54)	5884 (5.13)
Cigarette smoking				
No	1 544 424	2771 (0.18)	6235 (0.40)	62 448 (4.07)
1-9 cigarettes/d	146 829	389 (0.26)	894 (0.61)	7485 (5.14)
≥10 cigarettes/d	68 542	245 (0.36)	487 (0.71)	4134 (6.10)
Data missing	98 027	845 (0.86)	1022 (1.05)	6464 (6.72)
Hypertensive disease				
No	1 794 592	3498 (0.19)	6303 (0.35)	70 384 (3.94)
Preeclampsia	51 561	635 (1.23)	2038 (4.00)	8925 (18.26)
Pregestational hypertension	11 669	117 (1.00)	297 (2.57)	1222 (10.86)
Diabetic disease				
No	1 832 612	4183 (0.23)	8370 (0.46)	77 747 (4.27)
Gestational diabetes	17 278	42 (0.24)	122 (0.71)	1388 (8.11)
Pregestational diabetes	7932	25 (0.32)	146 (1.85)	1396 (17.99)
Year of delivery				
1992-1996	529 004	1112 (0.21)	2478 (0.47)	23 553 (4.48)
1997-2001	424 305	967 (0.23)	2026 (0.48)	18 387 (4.36)
2002-2006	482 492	1133 (0.23)	2268 (0.47)	21 015 (4.39)
2007-2010	422 021	1038 (0.25)	1866 (0.44)	17 576 (4.19)

[a] The study population included 1 857 822 deliveries of live singleton infants. Information about early pregnancy BMI was available in 86% (1 599 551 deliveries) of all deliveries.
[b] The rates of delivery at 22 to 27 weeks were calculated by comparison with all other deliveries, the rates of delivery at 28 to 31 weeks were calculated by comparison with deliveries at 28 weeks or later, and the rates of delivery at 32 to 36 weeks were calculated by comparison with deliveries at 32 weeks or later. Rates of preterm deliveries in proportion to the total number of women in the study were 0.23% for the 4250 born at 22 to 27 weeks, 0.47% for the 8638 born at 28 to 31 weeks, and 4.36% for the 80 531 born at 32 to 36 weeks.

Because information about BMI in early pregnancy was missing in 14% of all deliveries, supplemental analyses after multiple imputations were performed. BMI category was imputed using an ordinal logistic regression model with gestational age, maternal age, parity, calendar year of birth, and presence of the different obesity-related maternal diseases as predictors. After BMI category was imputed, missing values for the categorical variables of height, smoking, education, and mother's country of birth were imputed sequentially with ordinal logistic regression models where the variables in the sequence already imputed were added as predictors in the imputation model. Ten imputed data sets were created and analyzed by logistic regression applying the generalized estimating equation method when estimating parameters and covariance matrices, which then were analyzed by the procedure MIANALYZE. We restricted these analyses to risks of extremely, very, and moderately preterm delivery and risk of spontaneous extremely, very, and moderately preterm delivery.

A potential effect modification of height on the associations between BMI and risks of preterm delivery was also investigated. Analyses were stratified by maternal height, and ORs of extremely, very and moderately preterm delivery were calculated per unit effect of BMI. Underweight women were excluded.

A 2-tailed *P*-value of less than .05 (corresponding with 95% CIs of ORs not including unity) was used as the threshold for statistical significance. All statistical analyses were performed with SAS statistical software version 9.3, using procedures GENMOD, MI, and MIANALYZE (SAS Institute, Inc).

RESULTS

The Birth Register recorded information for 1 863 768 live singleton births between 1992 and 2010. After excluding 3942 births to women with an incomplete national registration number and 2004 women with missing data on gestational age, the study population included 1 857 822 deliveries of live singleton infants. Information about early pregnancy BMI was available in 86% (1 599 551 deliveries) of all deliveries (Table 1 and Table 2).

During the study period, there were 93 419 (5.03%) preterm (≤36 weeks) deliveries. Overall rates of extremely (22-27 weeks), very (28-31 weeks), and moderately (32-36 weeks) preterm deliveries were 0.23%, 0.47%, and 4.36%, respectively. Preterm delivery rates increased with BMI among overweight and obese women and were also increased among short women (<155 cm). Higher rates of preterm delivery were seen among teenage and older women (≥35 years), women having their first or at least their fourth childbirth, smokers, women with low education, and women born outside of Nordic countries. Maternal diseases, especially preeclampsia and pregestational hypertension, were associated with increased rates of preterm delivery (Table 1 and Table 2).

Rates of overweight and obesity were increased among short, older, multiparous (≥4), and lower-educated women. Rates of overweight and obesity were substantially increased in women with hypertensive or diabetic diseases. Women with missing information on smoking, education, or country of birth also had high rates of missing information on BMI. Women with obesity-related diseases did not have high rates of missing information on BMI (eTable 1, available at http://www.jama.com).

Table 2. Maternal Demographic Characteristics and Rates of Preterm Singleton Deliveries in Sweden 1992-2010

	No. of Women (n = 1 857 822)[a]	Weeks Gestation, No. (%)		
		22-27 (n = 4250)[b]	28-31 (n = 8638)[b]	32-36 (n = 80 531)[b]
Age, y				
≤19	36 035	141 (0.39)	232 (0.65)	2102 (5.89)
20-24	280 341	645 (0.23)	1265 (0.45)	13 328 (4.79)
25-29	616 455	1191 (0.19)	2580 (0.42)	25 829 (4.22)
30-34	603 441	1267 (0.21)	2693 (0.45)	24 237 (4.04)
≥35	321 550	1006 (0.31)	1868 (0.58)	15 035 (4.72)
Education, y				
≤9	185 791	615 (0.33)	1128 (0.61)	9572 (5.20)
10-11	381 530	976 (0.26)	1964 (0.52)	18 083 (4.78)
12	445 972	984 (0.22)	1994 (0.45)	19 531 (4.41)
13-14	272 545	569 (0.21)	1189 (0.44)	10 874 (4.02)
≥15	537 102	967 (0.18)	2126 (0.40)	20 552 (3.85)
Data missing	34 882	139 (0.40)	237 (0.68)	1919 (5.56)
Mother's country of birth				
Nordic[c]	1 546 445	3238 (0.21)	7020 (0.45)	66 519 (4.33)
Non-Nordic	291 432	909 (0.31)	1446 (0.50)	12 716 (4.40)
Data missing	19 945	103 (0.52)	172 (0.87)	1296 (6.59)

[a] The study population included 1 857 822 deliveries of live singleton infants. Information about early pregnancy BMI was available in 86% (1 599 551 deliveries) of all deliveries.
[b] The rates of delivery at 22 to 27 weeks were calculated by comparison with all other deliveries, the rates of delivery at 28 to 31 weeks were calculated by comparison with deliveries at 28 weeks or later, and the rates of delivery at 32 to 36 weeks were calculated by comparison with deliveries at 32 weeks or later. Rates of preterm deliveries in proportion to the total number of women in the study were 0.23% for the 4250 born at 22 to 27 weeks, 0.47% for the 8638 born at 28 to 31 weeks, and 4.36% for the 80 531 born at 32 to 36 weeks.
[c] Includes Sweden, Denmark, Finland, Iceland, and Norway.

BMI and Risks of Preterm Delivery by Gestational Age

Compared with women having normal BMI, risks of extremely, very, and moderately preterm deliveries increased with BMI (FIGURE). The overweight and obesity-related risks were highest for extremely preterm delivery and lowest for moderately preterm delivery. Among normal-weight women (BMI, 18.5-24.9), the rate of extremely preterm delivery was 0.17%. Compared with normal-weight women, rates and adjusted ORs (AORs) of extremely preterm delivery were as follows: BMI 25 to less than 30 (0.21%; AOR, 1.23; 95% CI, 1.13-1.35), BMI 30 to less than 35 (0.27%; AOR, 1.53; 95% CI, 1.35-1.74), BMI 35 to less than 40 (0.35%; AOR, 1.97; 95% CI, 1.62-2.40), and BMI of 40 or greater (0.52%; AOR, 2.91; 95% CI, 2.21-3.83). Compared with normal-weight women, underweight women (BMI<18.5) had slightly increased risks of very and moderately preterm deliveries. Supplemental analyses using multiple imputation of participants with missing values on BMI and covariates resulted in modest changes in risks, which were most pronounced for extremely preterm delivery; risks were slightly increased in underweight women and attenuated in obese women, especially in women with grade 3 obesity (Figure).

We also analyzed risks of preterm delivery in a subsample from which we had information on gestational age estimated both by ultrasound and by the last menstrual period (76% of all deliveries). When gestational age was estimated by ultrasound, the BMI-related risks of extremely preterm deliveries were essentially similar to those presented in the Figure. When the last menstrual period was used, the risks of preterm delivery related to overweight and obesity were slightly lower (eTable 2).

Among women with information about gestational length at first prenatal visit (recorded from 1996 forward), 90% underwent their first prenatal visit in the first trimester (within 14 completed weeks). Compared with results presented in the Figure, similar associations between BMI and risks of extremely, very, and moderately preterm delivery were obtained when only women with information on BMI recorded in the first trimester were included in the analyses (eTable 3).

In analyses of BMI and risk of preterm delivery stratified by maternal height, the results suggested no effect modification by height for extremely preterm delivery. The overall estimated risks for very and moderately preterm delivery were almost identical to the effect of BMI in the central 50% of the height distribution, while slightly stronger and weaker associations were observed among tall and short women, respectively (eTable 4).

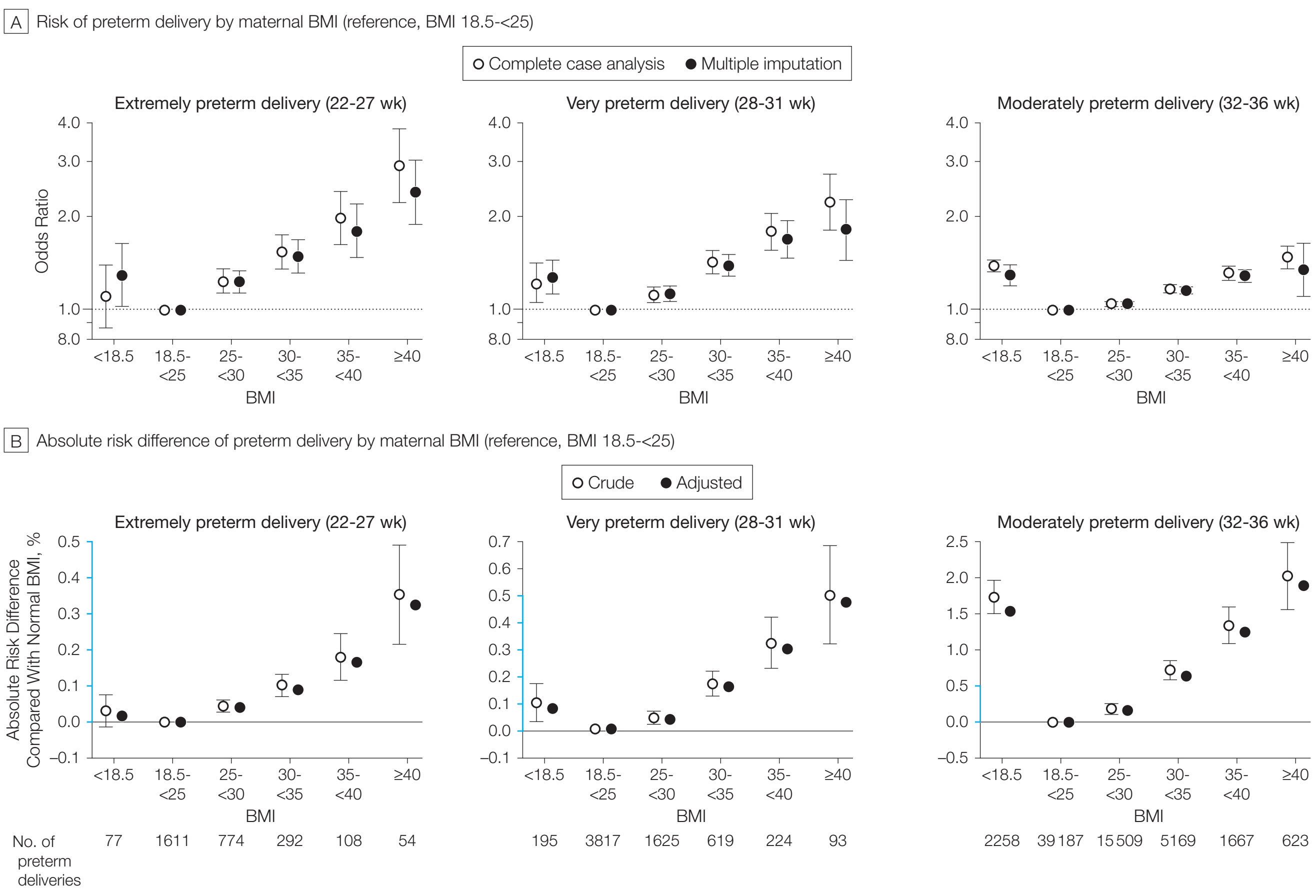
BMI and Obstetric Precursors of Preterm Delivery

For the 1 599 551 deliveries with data on early pregnancy BMI, information about precursors of preterm delivery was available in 1 573 003 (98%) deliveries. Compared with women with normal BMI, risks of spontaneous extremely preterm delivery increased with increasing obesity (TABLE 3). Using multiple imputation resulted in attenuated risks for women with severe obesity (BMI≥35). Risks of spontaneous very or moderately preterm delivery were generally not associated with obesity.

Compared with women with normal BMI, women with grade 2 and grade 3 obesity had increased risks of extremely preterm delivery because of premature rupture of the membranes and spontaneous labor (eTable 5). Risks of moderately preterm delivery due to premature rupture of the membranes modestly increased with BMI, but there were no associations between BMI and risks of very or moderately spontaneous preterm labor. When women with obesity-related disorders (hypertensive and diabetic diseases) were excluded, BMI-related rates and ORs of spontaneous extremely, very, and moderately preterm delivery were essentially unchanged (eTable 6).

Compared with women of normal BMI, risks of medically indicated extremely, very, and moderately preterm deliveries increased with BMI (TABLE 4). When pregnancies with obesity-related disorders were excluded (4.6% of the study population), the number of medically indicated extremely and very preterm deliveries were reduced by 60%, the number of medically indicated moderately preterm deliveries was reduced by 45%, and the BMI-related risks of medically indicated preterm deliveries were eliminated or were substantially reduced (Table 4).

Figure. Maternal BMI in Early Pregnancy and Risks of Preterm Delivery



A, Odds ratios (ORs) were estimated both from the data set with complete covariate information and after multiple imputation of missing values. ORs were adjusted for maternal age, parity, smoking, education, maternal height, maternal country of birth, and year of delivery. B, Absolute risks attributable to body mass index (BMI) were estimated from ORs in the complete case analysis. Y-axis scale shown in blue indicates range from 0% to 0.5%.

Table 3. Maternal BMI in Early Pregnancy and Risks of Spontaneous Preterm Delivery

	BMI Categories, Adjusted OR (95% CI)[a]					
	<18.5	18.5-<25	25-<30	30-<35	35-<40	≥40
Extremely preterm delivery[b]						
No. (%)	58 (0.14)	1200 (0.12)	536 (0.14)	181 (0.16)	74 (0.23)	38 (0.35)
Complete analyses[b]	1.03 (0.78-1.37)	1 [Reference]	1.12 (1.00-1.24)	1.22 (1.04-1.44)	1.73 (1.35-2.21)	2.71 (1.95-3.78)
Multiple imputation analyses[c]	1.19 (0.92-1.54)	1 [Reference]	1.12 (1.01-1.24)	1.21 (1.03-1.43)	1.57 (1.24-1.99)	2.07 (1.58-2.70)
Very preterm delivery[b]						
No. (%)	144 (0.35)	2246 (0.22)	822 (0.21)	288 (0.25)	96 (0.30)	29 (0.27)
Complete analyses[c]	1.36 (1.13-1.64)	1 [Reference]	0.95 (0.88-1.04)	1.08 (0.95-1.22)	1.25 (1.01-1.54)	1.08 (0.74-1.58)
Multiple imputation analyses[d]	1.35 (1.14-1.60)	1 [Reference]	0.96 (0.88-1.04)	1.07 (0.94-1.21)	1.19 (0.97-1.47)	1.02 (0.75-1.40)
Moderately preterm delivery[b]						
No. (%)	1858 (4.52)	30 425 (3.02)	11 353 (2.97)	3503 (3.09)	1077 (3.34)	374 (3.50)
Complete analyses[c]	1.41 (1.34-1.49)	1 [Reference]	0.99 (0.97-1.01)	1.02 (0.98-1.06)	1.08 (1.01-1.15)	1.14 (1.02-1.27)
Multiple imputation analyses[d]	1.31 (1.21-1.41)	1 [Reference]	0.98 (0.96-1.01)	1.01 (0.98-1.05)	1.06 (1.00-1.13)	1.13 (0.95-1.33)

Abbreviations: BMI, body mass index; OR, odds ratio.
[a] Adjusted for maternal age, parity, cigarette smoking, education, maternal height, maternal country of birth, and year of delivery. BMI was calculated as weight in kilograms divided by height in meters squared. Data are shown as adjusted OR (95% CI) unless otherwise indicated.
[b] Extremely preterm delivery, 22 to 27 weeks; very preterm delivery, 28 to 31 weeks; and moderately preterm delivery, 32 to 36 weeks.
[c] Analyses only include observations with complete information about covariates. In analyses of extremely preterm deliveries, the total number of deliveries was 1 544 662. The numbers of deliveries in each BMI category were 39 543 (BMI <18.5), 981 657 (BMI, 18.5-<25), 371 519 (BMI, 25-<30), 110 044 (BMI, 30-<35), 31 438 (BMI, 35-<40), and 10 461 (BMI ≥40). The number of events in the analysis of extremely preterm spontaneous delivery was 1967. In analyses of very preterm deliveries, the total number of deliveries was 1 541 746. The numbers of deliveries in each BMI category were 39 466 (BMI <18.5), 980 046 (BMI, 18.5-<25), 370 745 (BMI, 25-<30), 109 752 (BMI, 30-<35), 31 330 (BMI, 35-<40), and 10 407 (BMI ≥40). The numbers of events in the analysis of very preterm spontaneous delivery was 3440. In analyses of moderately preterm deliveries, the total number of deliveries was 1 535 173. The numbers of deliveries in each BMI category were 39 271 (BMI <18.5), 976 229 (BMI, 18.5-<25), 369 120 (BMI, 25-<30), 109 133 (BMI, 30-<35), 31 106 (BMI, 35-<40), and 10 314 (BMI ≥40). The number of events in the analysis of moderately preterm spontaneous delivery was 46 680.
[d] Indicates analyses with all observations using multiple imputation for observations with missing values.

DISCUSSION

In our nationwide cohort study of more than 1.5 million deliveries with information on early pregnancy BMI, we found that maternal overweight and obesity during pregnancy were associated with increased risk for preterm delivery. The highest risks were observed for extremely preterm deliveries. Specifically, compared with normal-weight women (BMI, 18.5-<25), women with grade 2 and 3 obesity (BMI≥35) had 0.2% to 0.3% higher rates of extremely preterm delivery and 0.3% to 0.4% higher rates of very preterm delivery. As previously reported,[6,7,10] this study also found that risk of moderately preterm delivery was increased among underweight women.

To our knowledge, this is the first study investigating the effect of overweight and obesity on risks of spontaneous and medically indicated extremely preterm deliveries. Overweight and obesity were associated with increased risks of medically indicated preterm deliveries at all gestational ages, while a dose-response relation between severity of obesity and risk of spontaneous preterm delivery was restricted to extremely preterm delivery. When pregnancies with obesity-related disorders were excluded, there were reductions in rates and risks of medically indicated but not spontaneous preterm deliveries. This is in line with results from previous investigations,[6,7] suggesting that obesity-related excess risks of medically indicated preterm deliveries may largely be due to obesity-related pregnancy disorders. In addition, the association between BMI and risk of moderately preterm delivery was larger in short women than in taller women. As the BMI-related increased risk of moderately preterm delivery was largely restricted to medically indicated preterm delivery, high BMI may be associated with higher risks of medically indicated moderately preterm delivery in short women than in taller women.

In spontaneous preterm deliveries, there are increased levels of inflammatory proteins (cytokines) such as interleukin 6, interleukin 1β, and tumor necrosis factor (TNF) α.[16] These cytokines are associated with cervical ripening and may also cause both weakening of the membranes and preterm myometrial contractions, probably through stimulation of prostaglandin production and matrix-degrading enzymes.[11,17,18] Mechanisms by which maternal stress, smoking, vaginal bleeding, and infections influence risk of preterm delivery involve maternal systemic or intrauterine inflammation.[10] Maternal obesity is associated with inflammatory up-regulation[19] through increased production of adipokines by adipose tissue and enhanced systemic secretion of proinflammatory cytokines.[20] In pregnancy, visceral fat mass is increased, particularly in obese women,[21] and adipokines from visceral fat are known to increase systemic inflammation.[22] Additional mechanisms that may contribute to preterm delivery in obese women include endothelial dysfunction, insulin resistance, oxidative stress, and lipotoxicity.[19,23] Visceral fatness is also accompanied by decreased insulin sensitivity and elevated levels of glucose.[24] The Hyperglycemia Adverse Pregnancy Outcome study[25] clearly demonstrated increasing risks of preterm delivery with increasing maternal glucose levels in women without diabetes.

Intrauterine bacterial infection is considered the most important risk factor for spontaneous extremely preterm delivery and often precedes both preterm premature rupture of the membranes and spontaneous preterm labor.[11,16] Most of these infections are subclinical and can lead to chorioamnionitis or induce other inflammatory responses.[11,16] Naeye reported that overweight and obesity were associated with increased rates of chorioamnionitis in preterm deliveries, and that this increase was larger at 24 to 30 weeks than at 31 to 37 weeks.[26] Obese women have increased risks of genital[27] and urinary tract infections,[28] which are recognized risk factors for chorioamnionitis. We hypothesize that an elevated inflammatory state may make obese women more prone to chorioamnionitis induced by subclinical infections, which further enhance inflammation and increase their risk of spontaneous extremely preterm delivery.

Strengths of our study include its large size, which allowed us to study risks of subgroups of preterm delivery and to study these risks in relatively small groups of women, such as in women with obesity grade 3 (BMI≥40). The inclusion of virtually all births in Sweden during the study period and the prospective data collection limits the possibilities of selection and recall bias. Besides the adjustment for confounders, standardized health care and the relatively homogeneous Swedish pregnant population should limit the possibilities of residual confounding and increase internal validity. Information about BMI, expected date of delivery, and whether delivery was spontaneous or medically indicated was recorded before delivery, and any misclassification should be nondifferential with respect to outcomes or exposures.

Information on gestational age was primarily based on early second trimester ultrasound measurements of fetal dimensions, and assessment of gestational age may have been more accurate with the use of first trimester ultrasonic scans.[29] Sarris et al[30] reported no influence of BMI on first trimester fetal growth, but we are unaware of any study investigating the corresponding association in the early second trimester. If maternal obesity is associated with excessive fetal growth early in the second trimester, we may have overestimated gestational age in obese women and therefore underestimated obesity-related risks of preterm delivery. When the last menstrual period was used to estimate gestational age, we found slightly lower risks of preterm delivery, compared with when information from early second trimester ultrasonic scans was used. However, using the last menstrual period to estimate gestational age may not be an ideal option since menstrual irregularities are more common in obese women than in women of normal weight.[31]

Table 4. Maternal BMI in Early Pregnancy and Risks of Medically Indicated Preterm Delivery

	BMI Categories					
	<18.5	18.5-<25	25-<30	30-<35	35-<40	≥40
All Women						
Extremely preterm delivery[a]						
No. (%)	17 (0.07)	395 (0.04)	226 (0.06)	108 (0.09)	35 (0.11)	17 (0.16)
Adjusted OR (95% CI)[b]	1.05 (0.63-1.74)	1 [Reference]	1.51 (1.27-1.79)	2.48 (1.99-3.1)	2.74 (1.92-3.92)	3.84 (2.32-6.38)
Very preterm delivery[a]						
No. (%)	60 (0.15)	1517 (0.15)	745 (0.19)	324 (0.28)	121 (0.37)	71 (0.66)
Adjusted OR (95% CI)[b]	0.97 (0.74-1.28)	1 [Reference]	1.29 (1.18-1.41)	1.91 (1.68-2.17)	2.52 (2.08-3.06)	4.16 (3.23-5.36)
Moderately preterm delivery[a]						
No. (%)	448 (1.09)	9006 (0.89)	4310 (1.13)	1725 (1.52)	618 (1.91)	256 (2.40)
Adjusted OR (95% CI)[b]	1.24 (1.12-1.37)	1 [Reference]	1.22 (1.18-1.27)	1.62 (1.54-1.71)	2.00 (1.84-2.18)	2.45 (2.15-2.79)
Women Without Hypertensive or Diabetic Diseases						
Extremely preterm delivery[a]						
No. (%)	11 (0.03)	168 (0.02)	84 (0.02)	34 (0.03)	11 (0.04)	4 (0.05)
Adjusted OR (95% CI)[b]	1.51 (0.78-2.90)	1 [Reference]	1.27 (0.96-1.67)	1.69 (1.15-2.5)	1.91 (1.02-3.56)	2.06 (0.75-5.64)
Very preterm delivery[a]						
No. (%)	38 (0.10)	673 (0.07)	263 (0.07)	97 (0.09)	19 (0.07)	17 (0.19)
Adjusted OR (95% CI)[b]	1.43 (1.02-1.99)	1 [Reference]	0.98 (0.84-1.13)	1.15 (0.92-1.44)	0.75 (0.47-1.2)	1.94 (1.18-3.19)
Moderately preterm delivery[a]						
No. (%)	300 (0.76)	5438 (0.56)	2215 (0.61)	745 (0.72)	233 (0.83)	87 (0.98)
Adjusted OR (95% CI)[b]	1.40 (1.24-1.59)	1 [Reference]	0.99 (0.94-1.04)	1.07 (0.99-1.16)	1.11 (0.97-1.28)	1.23 (0.99-1.53)

Abbreviations: BMI, body mass index; OR, odds ratio.
[a] Extremely preterm delivery, 22 to 27 weeks; very preterm delivery, 28 to 31 weeks; and moderately preterm delivery, 32 to 36 weeks.
[b] Adjusted for maternal age, parity, cigarette smoking, education, maternal height, maternal country of birth, and year of delivery. Analyses only include observations with complete information about covariates. In analyses of all women, the total numbers of deliveries and the number of deliveries in each BMI category were as reported in Table 2. In the analyses of all women, the number of events (medically indicated preterm deliveries) were 769 for extremely preterm delivery, 2725 for very preterm delivery, and 15 727 for moderately preterm delivery. In analyses of women without obesity-related disorders, the number of events were 301 for extremely preterm delivery, 1070 for very preterm delivery, and 8633 for moderately preterm delivery. In analyses of women without obesity-related disorders, the numbers of women with extremely preterm delivery were: 1 473 521 (total), 38 546 (BMI <18.5), 949 485 (BMI, 18.5-24.9), 350 248 (BMI, 25-<30), 99 528 (BMI, 30-<35), 27 074 (BMI, 35-<39), and 8640 (BMI ≥40); for women with very preterm delivery, 1 471 188 (total), 38 477 (BMI <18.5), 948 147 (BMI, 18.5-24.9), 349 643 (BMI, 25-<30), 99 318 (BMI, 30-<35), 26 999 (BMI, 35-<39), and 8604 (BMI ≥40); and for women with moderately preterm delivery, 1 466 574 (total), 38 308 (BMI <18.5), 945 272 (BMI, 18.5-24.9), 348 583 (BMI, 25-<30), 98 954 (BMI, 30-<35), 26 893 (BMI, 35-<39), and 8564 (BMI ≥40).

Information on maternal height was self-reported. Women tend to overreport height and the magnitude of an overreporting bias varies from 0.25 cm in US women[32] to 4 cm in Brazilian women.[33] Information on weight was based on measured weights, which is an advantage because self-reported weight is usually underestimated.[32] However, weight was measured at the first prenatal visit (for 90% in the first trimester), and the median gestational weight gain during the first trimester is estimated at 0.17 kg per week,[34] roughly corresponding with a 2 kg increase in weight during the first trimester. Thus, measurement errors in weight and height may have led us to slightly overestimate or underestimate BMI-related risks of preterm delivery.

Missing data may introduce bias when it is not random with respect to the outcome or covariates. Multiple imputation is one of a few techniques available to assess the potential bias introduced by missing data. Results from supplemental analyses using multiple imputation indicate that in our population, missing data were not likely to have resulted in substantial selection bias.

Information about weight at delivery was available in a subset of the population, but we decided not to study associations with weight gain. It was recently demonstrated that conventional measures of gestational weight gain may introduce reverse causation bias in studies of preterm delivery.[35] This is because preterm delivery, especially extremely preterm delivery, shortens the time women have to gain weight during pregnancy. Estimating the rate of weight gain by dividing the difference between delivery and booking weights (or self-reported prepregnancy weights) by gestational age is also suboptimal. Weight gain during pregnancy is not linear, the denominator for women with preterm delivery would be small, and their rates of weight gain would appear spuriously high. This might induce a biased positive relation between the rate of weight gain and extremely preterm delivery.[35]

Our results showing dose-response associations between maternal overweight and obesity and risks of preterm delivery, especially of extremely preterm delivery, suggest that maternal overweight and obesity may have serious long-term consequences for infant health. These results can be generalized to other populations with similar or higher rates of maternal obesity or preterm delivery inasmuch as the underlying pathways linking maternal obesity and preterm delivery are common across populations. In the United States, where preterm delivery rates are twice as high as in Sweden,[10] the majority of women are either overweight (26.0%) or obese (27.4%) in early pregnancy,[36] and severe obesity (BMI≥35) is much more common than in Sweden.[37] In 2008, extremely (<28 weeks) preterm births accounted for 0.60% of all live single births and 25% of all US infant deaths among singletons,[38] and extremely preterm birth is also the leading cause of long-term disability.[3,17] Considering the high morbidity and mortality among extremely preterm infants, even small absolute differences in risks will have consequences for infant health and survival. Even though the obesity epidemic in the United States appears to have leveled off,[37] there is a sizeable group of women entering pregnancy with very high BMI. Our results need to be confirmed in other populations given their potential public health relevance. Identifying the pathways through which maternal obesity influences offspring health is also needed to provide critical information to specifically target the women at highest risk of preterm delivery.

Author Contributions: Dr Cnattingius had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Villamor, Wikström, Granath, Cnattingius.
Acquisition of data: Cnattingius.
Analysis and interpretation of data: Cnattingius, Villamor, Johannson, Edstedt Bonamy, Persson, Wikström, Granath.
Drafting of the manuscript: Cnattingius, Villamor, Johannson, Edstedt Bonamy, Persson, Wikström, Granath.
Critical revision of the manuscript for important intellectual content: Villamor, Johansson, Edstedt Bonamy, Persson, Wikstrom, Granath.
Statistical analysis: Johansson, Cnattingius.
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Study supervision: Cnattingius.

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Online-Only Material: eTables 1 through 6 are available at http://www.jama.com.

REFERENCES

1. Aviram A, Hod M, Yogev Y. Maternal obesity: implications for pregnancy outcome and long-term risks—a link to maternal nutrition. *Int J Gynaecol Obstet*. 2011;115(suppl 1):S6-S10.
2. Simmons LE, Rubens CE, Darmstadt GL, Gravett MG. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. *Semin Perinatol*. 2010;34(6):408-415.
3. Hack M, Fanaroff AA. Outcomes of extremely immature infants—a perinatal dilemma. *N Engl J Med*. 1993;329(22):1649-1650.
4. McDonald SD, Han Z, Mulla S, Beyene J; Knowledge Synthesis Group. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. *BMJ*. 2010;341:c3428.
5. Torloni MR, Betrán AP, Daher S, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. *J Matern Fetal Neonatal Med*. 2009;22(11):957-970.
6. Khatibi A, Brantsaeter AL, Sengpiel V, et al. Prepregnancy maternal body mass index and preterm delivery. *Am J Obstet Gynecol*. 2012;207(3):e1-e7, e7.
7. 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.
8. Salihu H, Mbah AK, Alio AP, et al. Nulliparity and preterm birth in the era of obesity epidemic. *J Matern Fetal Neonatal Med*. 2010;23(12):1444-1450.
9. 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 [published online ahead of print April 5, 2013]. *PLoS ONE*. doi:10.1371/journal.pone.0060660/PONE-D-13-04948.
10. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
11. Behrman RE, Stith Butler A, eds. Preterm Birth: Causes, Consequences, and Prevention, 2007. http://www.ncbi.nlm.nih.gov/books/NBK11362/pdf/TOC.pdf. Accessed January 30, 2013.
12. The Swedish Centre for Epidemiology. The Swed-

ish Medical Birth Register: a summary of content and quality, 2003. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3_20031123.pdf. Accessed January 30, 2013.
13. World Health Organization. Global Database on Body Mass Index: BMI Classification. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed January 30, 2013.
14. Høgberg U, Larsson N. Early dating by ultrasound and perinatal outcome: a cohort study. *Acta Obstet Gynecol Scand*. 1997;76(10):907-912.
15. Tucker J, McGuire W. Epidemiology of preterm birth. *BMJ*. 2004;329(7467):675-678.
16. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. *BJOG*. 2006;113(suppl 3):17-42.
17. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000;342(20):1500-1507.
18. Romero R, Gomez R, Ghezzi F, et al. A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. *Am J Obstet Gynecol*. 1998;179(1):186-193.
19. 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):4231-4237.
20. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol*. 2004;15(11):2792-2800.
21. Soltani H, Fraser RB. A longitudinal study of maternal anthropometric changes in normal weight, overweight and obese women during pregnancy and postpartum. *Br J Nutr*. 2000;84(1):95-101.
22. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 2007;56(4):1010-1013.
23. Jarvie E, Hauguel-de-Mouzon S, Nelson SM, Sattar N, Catalano PM, Freeman DJ. Lipotoxicity in obese pregnancy and its potential role in adverse pregnancy outcome and obesity in the offspring. *Clin Sci (Lond)*. 2010;119(3):123-129.
24. Bartha JL, Marín-Segura P, González-González NL, Wagner F, Aguilar-Diosdado M, Hervias-Vivancos B. Ultrasound evaluation of visceral fat and metabolic risk factors during early pregnancy. *Obesity (Silver Spring)*. 2007;15(9):2233-2239.
25. Metzger BE, Lowe LP, Dyer AR, et al; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358(19):1991-2002.
26. Naeye RL. Maternal body weight and pregnancy outcome. *Am J Clin Nutr*. 1990;52(2):273-279.
27. Sebire NJ, Jolly M, Harris JP, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord*. 2001;25(8):1175-1182.
28. Nohr EA, Timpson NJ, Andersen CS, Davey Smith G, Olsen J, Sørensen TI. Severe obesity in young women and reproductive health: the Danish National Birth Cohort. *PLoS One*. 2009;4(12):e8444.
29. Caughey AB, Nicholson JM, Washington AE. First- vs second-trimester ultrasound: the effect on pregnancy dating and perinatal outcomes. *Am J Obstet Gynecol*. 2008;198(6):e1-e5.
30. Sarris I, Bottomley C, Daemen A, et al. No influence of body mass index on first trimester fetal growth. *Hum Reprod*. 2010;25(8):1895-1899.
31. Wei S, Schmidt MD, Dwyer T, Norman RJ, Venn AJ. Obesity and menstrual irregularity: associations with SHBG, testosterone, and insulin. *Obesity (Silver Spring)*. 2009;17(5):1070-1076.
32. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. *Matern Child Health J*. 2007;11(2):137-144.
33. Lucca A, Moura EC. Validity and reliability of self-reported weight, height and body mass index from telephone interviews. *Cad Saude Publica*. 2010;26(1):110-122.
34. Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. *Obstet Gynecol*. 2010;115(3):597-604.
35. Hutcheon JA, Bodnar LM, Joseph KS, Abrams B, Simhan HN, Platt RW. The bias in current measures of gestational weight gain. *Paediatr Perinat Epidemiol*. 2012;26(2):109-116.
36. Dalenius K, Brindley P, Smith B, Reinold C, Grummer-Strawn L. Pregnancy Nutrition Surveillance 2010 Report, Centers for Disease Control and Prevention, 2012. http://www.cdc.gov/pednss/pdfs/2010-PNSS-Summary-Report.pdf. Accessed January 30, 2013.
37. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307(5):491-497.
38. United States Department of Health and Human Services, Centers of Disease Control and Prevention, National Center for Health Statistics, Division of Vital Statistics. Linked Birth/Infant Death Records 2007-2009. CDC Wonder On-line Database. http://wonder.cdc.gov/lbd-current.html. Accessed January 30, 2013.

