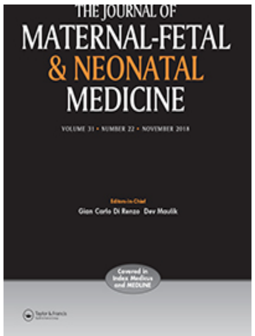


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ORIGINAL ARTICLE

# The effect of obesity on early fetal growth and pregnancy duration: a cohort study

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**ABSTRACT**

**Objective:** The objective of this study is to investigate the effect of maternal obesity on fetal size in first- and second-trimester pregnancies and to determine duration of pregnancy as estimated by a variety of methods.

**Methods:** Between 2006 and 2011, a cohort study included ($n = 9055$) singleton pregnancies that resulted in live birth at Holbaek Hospital in Denmark. This study recorded first- and second-trimester fetal measurements and maternal anthropometry. Characteristics considered included mother's age, parity, height, body mass index (BMI), smoking habits, and sex of child. The correlation between BMI and duration of pregnancy was analyzed by time-to-event analysis and accounted for medical intervention by censoring while correlation of BMI on fetal size was evaluated by multiple regression analysis.

**Results:** Adjusting for maternal and fetal characteristics, BMI was associated with prolonged pregnancy duration (0.20–0.22 d per kg/m$^2$ (standard error (SE) 0.02)) when using ultrasound and 0.26 d per kg/m$^2$ (SE: 0.03) when using last menstrual period. With increasing BMI, fetal biometries in first and second trimester were significantly smaller than expected (0.08 mm per kg/m$^2$ when measured by crown rump length (SE 0.02)).

**Conclusions:** Maternal BMI is correlated to smaller fetal size in early pregnancy and prolongs duration of pregnancy.

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**KEYWORDS**
Crown rump length; duration of pregnancy; fetal growth; obesity; ultrasound

## Introduction

The worldwide prevalence of obesity is increasing. Obesity among pregnant women has been associated with increased risk of adverse outcomes for both mother and infant [1,2]. Precise dating of pregnancy is critical for prenatal care (i.e. assessment of fetal growth by ultrasound (US)), interventions during pregnancy (i.e. induction due to a post-term pregnancy), and management of preterm birth.

Sex of child, parity, maternal age, smoking habits, low educational levels, and gestational age (GA) at time of US measurements have been shown to influence US dating [3–5]. Additionally, BMI's influence on crown rump length (CRL) in first trimester has been explored in a few small studies and no noticeable association has been found [6,7], although high maternal BMI is known to increase fetal growth in later stages of pregnancy [8]. High maternal BMI may postpone estimated delivery date. This is seen when using biparietal diameter (BPD) measurement in the second trimester and, as suggested by Simic et al. [9], is possibly due to systematic errors or incorrect US measurements.

On one hand, obese women have an increased risk of prolonged pregnancy compared with women of normal weight [10,11]; on the other hand, maternal obesity has also been found to increase the risk of preterm delivery [12]. In most studies, the duration of pregnancy has been determined by using a combination of dating methods (first and second trimester US and last menstrual period (LMP)) [10–12]. Consequently, the impact of maternal BMI on duration of pregnancy and its pathophysiological explanation is not clear.

The objectives of the present study were (1) to investigate the relationship between maternal BMI and

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duration of pregnancy and (2) to analyze first- and second-trimester fetal biometrics as a function of maternal BMI.

## Materials and methods

All pregnant women in Denmark are offered two US examinations. The first occurs between GA 11 + 0 to 14 + 0 weeks as part of risk estimation of trisomy 21. The second occurs between GA 18 + 0–21 + 0 weeks and screens for malformations.

Data were collected prospectively from 1 January 2006 to 31 December 2011 at Holbaek Hospital on the island of Zealand in Denmark. All pregnancies in which the CRL was between 45 and 85 mm during the first trimester were identified. This measurement was used for the estimation of GA as a part of routinely performed nuchal translucency examinations [13]. Multiple pregnancies, stillbirths, and late pregnancy losses were excluded as were pregnancies in which BMI, LMP, BPD, and/or head circumference (HC) were not recorded.

Data for this study were registered and stored in the Astraia database® which is composed of information about all US examinations performed on pregnant women during the study and includes mother's medical history, LMP, parity, prepregnancy maternal weight, and height as well as smoking and alcohol habits. The data were combined with the Danish Medical Birth Registry which contains data on all births in Denmark and includes information on date of birth, weight, length, sex of the child, multiple pregnancy, complications during pregnancy and birth, Apgar scores, and umbilical artery pH [14]. Prepregnancy weight and height of mother were used for the calculation of BMI and women were categorized as underweight (<18.5 kg/m$^2$), normal weight (18.5−24.99 kg/m$^2$), overweight (25−29.99 kg/m$^2$), moderately obese (30−34.99 kg/m$^2$), and severely obese (≥35 kg/m$^2$) [15].

In this study, GA was calculated using five different dating methods: (1) the first day of LMP, (2) CRL [16], (3) BPD in the interval of 19–30 mm – representing a GA of 11 + 0–14 + 6 weeks ($BPD_1$) [17], (4) BPD in the interval of 31–55 mm – representing a GA of 15 + 0–22 + 0 weeks ($BPD_2$) [17], and (5) HC in the interval of 110–200 mm – representing a GA of 15 + 0–22 + 0 weeks [17]. Duration of pregnancy was defined as number of days from first day of LMP to date of birth whereas duration of pregnancy when defined by US (for each method) calculated GA at the time of US examination plus the number of days to birth.

Outcomes of the study were (1) duration of pregnancy in women with spontaneous birth and (2) deviation of fetal size in early pregnancy.

In regard to duration of pregnancy, some pregnancies ended with labor induction or elective cesarean section. These observations were, in effect, partly censored and only the lower limit for duration of pregnancy was known. A Weibull-based time-to-event analysis was used to model duration until spontaneous birth with time to spontaneous delivery in days used as the event of interest and, thereby, censoring at time of induction or elective cesarean section. Clustering of more than one birth by the same mother was accounted for and variables were included in the time-to-event analysis to investigate their influence on estimated pregnancy length through different dating methods. These variables included maternal age (years), maternal height (cm), maternal BMI (kg/m$^2$), parity (number of pregnancies 1–9), smoking habits (smoker and non-smoker) as well as sex of child. The coefficients of the Weibull model can be interpreted as average change in days of pregnancy length per unit change in a specific covariate.

Evaluating fetal size in early pregnancy, subanalyses were performed on CRL and BPD measurements (mm) in first trimester and BPD and HC mm in second trimester, and only women with a regular and reliable LMP were included. Multiple regression analyses were used to assess the relationship between fetal size and mother's BMI. By using women with known LMP, GA by LMP was defined as the biological reference and deviations in mm for available US measurements (CRL, $BPD_1$, $BPD_2$, and HC). Adjustments were also made for fetal sex and mother's smoking habits. Additionally, multiple deliveries per mother were accounted for. The statistical analyses were performed using STATA (version 13, StataCorp LLC, College Station, TX).

This cohort study was reported in accordance with the STROBE recommendations and was approved by the Danish Data Protection Agency (6 June 2013 Reg no. SJ-HO-01) as well as the regional Research Ethics Board (3 April 2013 SJ-335).

## Results

During the study period, 14,593 women visited the US unit and later gave birth to a live child. Among these, 12,402 had a first trimester US. Out of that number, 3347 were excluded due to multiple pregnancies ($n = 530$), stillbirths or late intrauterine loss ($n = 63$), unregistered BMI ($n = 106$), and pregnancies in which LMP, BPD, and/or HC were not recorded ($n = 2648$). Thus, 9055 pregnancies were included in the analysis regarding pregnancy duration. In the subanalysis of evaluation fetal size, 5484 women were included. Maternal characteristics and mode of delivery in different BMI categories are summarized in Table 1.

Table 2 shows the effect on duration of pregnancy (change in days/unit) of different maternal and fetal characteristics in relation to five different dating methods. Increasing BMI was significantly associated with increased duration of pregnancy – 0.20–0.21 d/(kg/m$^2$) (standard error (standard error (SE) 0.02)) – when pregnancy was dated by US in the first and second trimester and 0.26 d/kg/m$^2$ (SE 0.03) when LMP was used. Thus, a discrepancy in BMI of 20 kg/m$^2$ (e.g. a BMI of 20 kg/m$^2$ compared with 40 kg/m$^2$) was associated with increase in the duration of pregnancy from 4.0 to 5.2 d depending on whether dating was based on US or LMP. Mother's height also influenced duration of pregnancy positively with a change of between 0.08 and 0.14 d/cm (SE 0.02) which implies an increase in the duration of pregnancy of 1.6–2.8 d when there is a height difference of 20 cm. There was no significant interaction between maternal height and BMI. The analysis also evaluated parity, mother's age, smoking habits, and fetal sex.

Table 3 displays the regression coefficients for BMI, fetal sex, and smoking habits. It represents influences on the size of the fetal biometrics (mm) in the first and second trimesters. In women with reliable and regular LMP, increasing BMI correlated with significantly smaller US fetal measurements than expected from their GA as estimated by LMP. For example, an increase of BMI of 20 kg/m$^2$ is associated with a 1.6 mm shorter CRL.

## Discussion

The researchers found that obese women had significantly smaller than expected US fetal biometries in the first and second trimesters. Furthermore, obese women had increased duration of pregnancy, and the researchers could quantify this association. An average of 4.0–5.2-d longer pregnancy was observed in women

**Table 1.** Characteristics of the study population stratified by maternal BMI.

| BMI | <18.5 | 18.5–24.99 | 25–29.99 | 30–34.99 | ≥35 | *n/N* |
|---|---|---|---|---|---|---|
| Number of mothers | 341 (3.8) | 5056 (55.8) | 2213 (24.4) | 976 (10.8) | 469 (5.2) | 9055 |
| Maternal age at delivery | 27 (23–31) | 29 (26–33) | 30 (26–33) | 29 (25–32) | 29 (25–33) | |
| Maternal height | 168 (163–172) | 168 (163–172) | 168 (163–172) | 168 (163–172) | 168 (163–172) | |
| Parity | | | | | | |
| 0 | 159 (4.7) | 1948 (57.1) | 790 (23.2) | 370 (10.9) | 143 (4.2) | 3410 |
| 1 | 118 (3.4) | 1939 (56.2) | 865 (25.1) | 244 (10.0) | 185 (5.4) | 3451 |
| 2 or more | 56 (3.0) | 1000 (53.9) | 481 (25.9) | 213 (11.5) | 105 (5.7) | 1855 |
| Missing | 8 (2.4) | 169 (49.9) | 77 (22.7) | 49 (14.5) | 36 (10.6) | 339 |
| Maternal smoking | | | | | | |
| Non-smoker | 243 (3.2) | 4221 (56.2) | 1866 (24.9) | 817 (10.9) | 362 (4.8) | 7509 |
| Smokers | 97 (6.3) | 829 (54.0) | 343 (22.4) | 159 (10.4) | 106 (6.9) | 1534 |
| Missing | 1 (8.3) | 6 (50.0) | 4 (33.3) | 0 (0) | 1 (8.3) | 12 |
| Sex of the child | | | | | | |
| Male | 171 (3.7) | 2618 (56.2) | 1146 (24.6) | 485 (10.4) | 239 (5.1) | 4659 |
| Female | 170 (3.9) | 2438 (55.5) | 1067 (24.3) | 491 (11.2) | 230 (5.2) | 4396 |
| Delivery mode[a] | | | | | | |
| Planed cesarean | 23 (6.7) | 440 (8.7) | 207 (9.4) | 105 (10.8) | 69 (14.7) | 844 |
| Emergency cesarean | 11 (3.2) | 104 (2.1) | 42 (1.9) | 39 (4.0) | 10 (2.1) | 206 |
| Induction of labor | 40 (11.7) | 705 (13.9) | 395 (17.8) | 242 (24.8) | 150 (32.0) | 1532 |
| Spontaneous birth | 267 (78.2) | 3807 (75.3) | 1569 (70.9) | 590 (60.5) | 240 (51.2) | 6473 |

Data are given as median (interquartile rage) or *n/N* (%). [a]Data are given as rates (%) of delivery modes/BMI-group.

**Table 2.** The influence of maternal characteristics and fetal sex on pregnancy duration in days analyzed by time-to-event analysis.

| | GA by CRL | | | GA by $BPD_1$ | | | GA by $BPD_2$ | | | GA by HC | | | GA by LMP | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Change in days | SE | *p* | Change in days | SE | *p* | Change in days | SE | *p* | Change in days | SE | *p* | Change in days | SE | *p* |
| Maternal BMI (kg/m$^2$) | 0.20 | 0.02 | <.001 | 0.20 | 0.02 | <.001 | 0.20 | 0.02 | <.001 | 0.22 | 0.02 | <.001 | 0.26 | 0.03 | <.001 |
| Maternal height (cm) | 0.10 | 0.02 | <.001 | 0.10 | 0.02 | <.001 | 0.14 | 0.02 | <.001 | 0.14 | 0.02 | <.001 | 0.08 | 0.02 | <.001 |
| Parity (number) | −0.12 | 0.12 | .325 | −0.19 | 0.12 | .132 | −0.60 | 0.13 | <.001 | −0.38 | 0.13 | .003 | 0.08 | 0.15 | .597 |
| Maternal age (years) | 0.13 | 0.02 | <.001 | 0.11 | 0.02 | <.001 | 0.13 | 0.03 | <.001 | 0.13 | 0.02 | <.001 | −0.08 | 0.03 | .005 |
| Sex (female) (yes/no) | 0.26 | 0.20 | .198 | −0.01 | 0.20 | .948 | −1.43 | 0.22 | <.001 | −1.18 | 0.21 | <.001 | 0.54 | 0.24 | .027 |
| Smoker (yes/no) | −1.00 | 0.27 | <.001 | −0.96 | 0.27 | <.001 | −1.11 | 0.29 | <.001 | −1.01 | 0.28 | <.001 | −0.31 | 0.33 | .340 |

BMI: body mass index; GA by CRL: gestational age defined by crown rump length; GA by $BPD_1$: gestational age defined by biparietal diameter measured in first trimester; $BPD_2$: gestational age defined by biparietal diameter measured in second trimester; GA by HC: gestational age defined by head circumference; GA by LMP: gestational age defined by last menstrual period; SE: standard error; *p*: *p* value; change in days: coefficient interpreted as change in days per unit.

Table 3. The influence of maternal BMI, sex of the fetus, and smoking habit on fetal biometrical measurements in mm by multiple regression analysis.

| | CRL | SE | $p$ | $BPD_1$ | SE | $p$ | $BPD_2$ | SE | $p$ | HC | SE | $p$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mothers BMI ($kg/m^2$) | −0.08 | 0.02 | <.001 | −0.03 | 0.01 | <.001 | −0.03 | 0.01 | <.001 | −0.06 | 0.02 | .005 |
| Sex (female) (yes/no) | −0.69 | 0.17 | <.001 | −0.30 | 0.05 | <.001 | −1.01 | 0.06 | <.001 | −3.22 | 0.20 | <.001 |
| SMoNSmon-Smoker (yes/no) | −1.02 | 0.23 | <.001 | −0.14 | 0.07 | .043 | −0.23 | 0.09 | .008 | −0.86 | 0.28 | .002 |

CRL: crown rump length; $BPD_1$: biparietal diameter in the first trimester; $BPD_2$: biparietal diameter in the second trimester; HC: head circumference; SE: standard error; $p$: $p$ value.

with BMI of 40 $kg/m^2$ when compared with women with BMI of 20 $kg/m^2$. This casually leads to increased post-term rate and, when guidelines regarding earlier labor induction in obese women are used, increased induction rates.

A strength of this study is the large and unselected population which had a high frequency of overweight and obese women (24% and 16%, respectively). Another advantage is the use of time-to-event analysis to account for censoring of time to spontaneous birth by labor induction and prelabor cesarean section. The time-to-event analysis is important as frequency of these interventions increases among obese women [2,18]. Induction rate among severely obese women in this study was 32% compared with 14% in pregnant women of normal weight (Table 1). Exclusion from the analysis of women with prelabor interventions would have exposed the results to severe selection bias which would have lowered BMI's effect on duration of pregnancy.

The use of time-to-event analysis is uncommon in obstetrics research and should be employed more due to the increase of medical interventions. It constitutes a separate contribution to the study by achieving the most accurate estimate of BMI's effect on pregnancy duration. Finally, when evaluating the influence of different fetal and maternal characteristics on pregnancy duration, the dating method must be considered. We have previously described that different dating methods in first and second trimesters exhibit systematic discrepancies that affect post-term rate [19]. Thus, to avoid this bias, the individual methods must be evaluated separately.

There are limitations to this study. Although certified personnel performed all examinations, interobserver variability cannot be excluded. Measurement of CRL and BPD during the first trimester was found to show small interobserver variation in our department (unpublished data) and in the literature [20]. Only women with reliable and regular LMP in the subanalysis of fetal size were included. The women's menstrual history was registered during first-trimester examination which may have resulted in recall bias if obese women reported LMP differently than non-obese women. This, however, is unlikely.

In regard to the performance of the different dating methods, a discrepancy in pregnancy duration estimated by US compared with LMP in relation to BMI was found. This was also found by Simic et al. [9] when it was demonstrated that increasing BMI was related to postponement of due date when US biometrics in second trimester (BPD) compared with LMP were used. The author suggested that this finding was caused by measurement error which could be increased among obese women. In the present study, the same discrepancy between US and LMP was found; moreover, this discrepancy was also present in first trimester. The reason for this may either be that fetuses are measured smaller in women with high BMI due to a systematic measurement error, or that the fetuses really are smaller. In both first and second trimesters, significantly smaller fetal biometrics was observed which supports a true difference between LMP and US dating. When combined with the fact that the effect of obesity on BPD in the first and second trimesters was equal (Table 3), we do not believe that measurement error is responsible for the observed smaller fetuses. First trimester biometric dating has been found to have smaller measurement error compared with second trimester measurements [19,21] and different transducer placements are used in first trimester (low abdominal and transvaginal) compared with second trimester (infraumbical) where the abdominal fat layers have different depths. If measurement error due to abdominal fat were to explain the difference in due date between ultrasound and LMP, a discrepancy between first and second trimester measurement would be expected.

Few studies have addressed the impact of maternal BMI on early fetal growth. Sarris et al. [7] found no association; however, this particular study only included 30 women with a BMI above 30 $kg/m^2$, and the authors mentioned that the study could be underpowered. Mook-Kanamori et al. [6] studied different parameters that may affect CRL. This study found that BMI had a negative influence on CRL but the difference was not significant. It only included women with a median BMI of 23.5 $kg/m^2$, and the maximal BMI was 32 $kg/m^2$. Two other studies have found similar results in diabetic women [22,23]. The authors suggested that this finding of smaller fetuses during the first trimester could be due to a growth delay or late implantation. Both diabetic and obese women exhibit insulin resistance that promotes an abnormal metabolic state that might impair fetal growth and, thus, give rise to our findings. Whether smaller fetal size is caused by late implantation or a general impairment of growth needs to be further investigated.

The mechanism behind prolonged duration of pregnancy in obese women is unknown. It might be explained by different endocrine factors such as hormone metabolism in the adipose tissue or decreased responsiveness to labor mediators [11]. Obese women more often have labor abnormalities such as prolonged latent phases and first stage of labor, greater need for oxytocin, and higher rates of cesarean delivery. It has been hypothesized that this could be due to inadequate myometrium contraction patterns or decreased receptiveness to oxytocin [24]. In some countries, obesity is a medical indication for induction at 41 weeks of gestation due to the assumption that an obese pregnancy is a high-risk pregnancy with a higher rate of mortality and morbidity [25]; however, whether this practice is beneficial has not yet been fully investigated. The fact that increasing BMI is related to increased pregnancy length emphasizes the need for investigating the optimal gestational age and method for labor induction in obese women so that rates of failed induction and cesarean section are minimized.

In conclusion, this study found that high maternal BMI prolonged pregnancy duration. This finding was independent of different US methods used for the dating of pregnancy but was more pronounced when dating was based on LMP. The difference between LMP and US was explained by correlation of increasing maternal BMI to smaller fetal size in first as well as second trimester. Further studies are needed to evaluate possible biological factors influencing growth in early pregnancy and to identify the most appropriate GA for labor induction in obese women.

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