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CHAPTER 3

Is short first-trimester crown-rump length associated with spontaneous preterm birth?

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ABSTRACT

Objective

To assess the association between first trimester crown-to-rump length (CRL) and the risk of spontaneous preterm birth before 32 weeks' gestation.

Methods

We performed a matched case-control study of 129 women with spontaneous preterm birth at <32 weeks' gestation (cases) and 129 women with term deliveries (controls) using data stored in the ultrasound and obstetric databases of our tertiary referral center. Cases and controls were individually matched based on maternal age, parity, history of preterm birth and medical indication for antenatal care. Fetal CRL measured between 8+0 and 13+6 weeks was expressed as multiples of the median (MoM) expected CRL, based on last menstrual period. We investigated the association between CRL-MoM and spontaneous preterm birth using logistic regression analysis.

Results

CRL-MoM was not associated with spontaneous preterm birth: odds ratio (OR) 1.10 (95% CI, 0.89 - 1.36) per 0.10 MoM increase in CRL. Timing of measurement did not influence the model (P=0.59). This was confirmed when restricting the analysis to the 93 pairs with CRL measurements made between 10+0 and 13+6 weeks: OR for preterm birth 1.07 (95% CI 0.83 - 1.37) per 0.10 MoM increase in CRL.

Conclusion

A short CRL in the first trimester is not associated with spontaneous preterm birth before 32 weeks' gestation thus short CRL cannot be used to identify women at increased risk of preterm birth.

INTRODUCTION

Preterm birth is the leading cause of perinatal mortality and morbidity.[1] Worldwide, about 27% of almost four million annual neonatal deaths are directly caused by preterm births and many others are due to the consequences of preterm birth, in particular infection.[2] Moreover, preterm birth has a tremendous emotional impact on parents[3] and poses an economic burden on society.[4] For 2005, it was estimated that the cost in the USA alone in terms of medical and educational expenditure and lost productivity associated with preterm birth was more than $26 billion.[5] Accurate identification of those at increased risk for spontaneous preterm birth may allow for timely allocation of preventative or therapeutic strategies. Consequently, detection of reliable predictors, preferably those that can be used in early pregnancy, is crucial.

Recent studies have found that fetuses who have a crown-to-rump length (CRL) that is shorter than would be expected based on the gestational age calculated from the last menstrual period (LMP) have a shorter duration of pregnancy[6] and are at increased risk for preterm birth.[7,8] Yet, in these studies a distinction between spontaneous preterm birth and indicated preterm birth, due to maternal disease, fetal distress or signs of placental insufficiency, was not made. It is not known whether the reported association can be entirely explained by the indicated preterm births, or whether it remains valid in cases of spontaneous preterm birth only. It might be that the association between short CRL and preterm birth reflects fetuses in which growth restriction is already present in early pregnancy [9] and that are subsequently born preterm because of obstetric complications, as opposed to those born after spontaneous onset of preterm labor. In this study we investigated the association between short first-trimester CRL and preterm birth in a population of only spontaneous preterm births.

METHODS

We performed a case-control study among women who delivered between January 2000 and May 2010 in the Academic Medical Center, a Dutch tertiary referral hospital. All data were collected during routine antenatal care and stored in the hospital's ultrasound and obstetric care databases.

This study was exempt from Institutional Review Board (IRB) approval. The Dutch Medical Research Involving Human Subjects Act states that IRB approval is only required when patients are subjected to an intervention, and thus was not mandatory for this observational study using data collected during routine antenatal care.

Since our hospital is a tertiary referral center, most women attending antenatal care in our center are at increased risk for pregnancy complications or have pre-existing medical conditions that call for specialized antenatal surveillance. However our hospital also has a regional function for the surrounding area. As a consequence, our population also consists of low-risk women who prefer to deliver in a hospital instead of having a home birth, without additional medical indications. Some of these women are referred to our hospital for their routine ultrasound examinations, so these women could be used as a match for low-risk women transferred at the time of preterm labor.

Eligible were women of 18 years or over with a singleton pregnancy who underwent an ultrasound measurement of fetal CRL between 8+0 and 13+6 weeks' gestation, had a regular menstrual cycle of 28 ± 4 days and a certain first day of their LMP. Pregnancies with fetal congenital anomalies or those resulting in intrauterine fetal death were excluded. Women with spontaneous preterm births, defined as births between 24+0 and 32+0 weeks' gestation, were selected for the case group. Controls were selected from women who delivered at term (37+0 to 41+6 weeks), after spontaneous onset of labor. Each case was individually matched to one control for maternal age (≥35 or <35 years), parity (nulliparous or parous), history of preterm birth (present or absent) and medical indication for antenatal care. When multiple controls were suitable to match one case, the control was randomly selected. Each case-control pair was given a unique match number. Data of cases and controls were retrieved from the obstetrical care database and supplemented with data collected from the ultrasound database and labor ward records.

The estimated date of delivery and gestational age at ultrasound scan were recalculated using the LMP. We estimated the expected CRL at the time of the ultrasound examination based on the recalculated gestational age at ultrasound using the equation of Robinson and Fleming.[10] The measured CRL was expressed as multiples of the median (MoM) expected CRL and calculated by dividing the measured CRL by the median expected CRL from Robinson's equation. We decided to express the CRL in MoM's instead of the more commonly used Z-scores because Robinson's equation gives a point estimate for CRL, but no distribution in terms of standard deviation or confidence interval. We could not calculate z-scores since their calculation requires knowledge of the standard deviation.

If the MoM of a case deviated more than three standard deviations from the mean MoM of women with a normal pregnancy outcome (controls), the corresponding case-control pair was excluded from analysis because these findings are unlikely and suggestive of an uncertain or wrong LMP or typing errors in the medical records.

Maternal and fetal characteristics were compared between the case and control groups with a paired *t*-test, Wilcoxon signed rank test, McNemar test or chi-square test, as appropriate. We investigated the association between CRL-MoM and spontaneous preterm birth. We performed logistic regression analysis with a fixed effect for CRL-MoM as a continuous variable and a random intercept for match number, which estimated the effect of CRL-MoM given the matched-paired structure of the dataset.[11] Regression analysis was performed both unadjusted and adjusted for maternal age, parity and medical indication for antenatal care, to control for selection bias introduced by matching.[12] In addition we adjusted for ethnicity,[13] smoking[14] and fetal sex,[15] factors known to influence CRL, and timing of CRL measurement (which could have affected reliability of the measurement). We repeated the analyses including only women with CRLs measured from 10 weeks onward. To illustrate the association found, we compared the percentages of fetuses with short CRLs, defined as CRL-MoM below the 5th, 10th or 20th percentile of the study population, respectively, between the preterm birth (or case) group and the term delivery (or control) group. Statistical analyses were performed using PASW Statistics 18.0 and R version 9.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified a total of 132 eligible women with spontaneous preterm births before 32 weeks' gestation who had had CRL measured in the period between January 2000 and May 2010 and for whom all data were available. These cases were matched to 132 controls (Figure 1). We excluded three case-control pairs because their MoM values differed by more than three standard deviations from the mean MoM of women with normal pregnancy outcomes (the controls). In all pairs the CRL-MoM of the case with preterm birth was outside the specified range: in two cases the MoM was larger than would be expected, in one case it was smaller than would be expected. Thus, 129 cases and 129 controls were included in the analyses. None of the patients in our population was diagnosed with pre-eclampsia or severe fetal growth restriction (defined as birth weight below the 5th percentile). Maternal and fetal characteristics of the group are shown in Table 1. Twenty-five neonates died in the preterm birth (case) group, of whom 13 were born at a gestational age of less than 26 weeks, compared to none in the term birth (control) group. Causes of death were mostly respiratory insufficiency or severe infection.

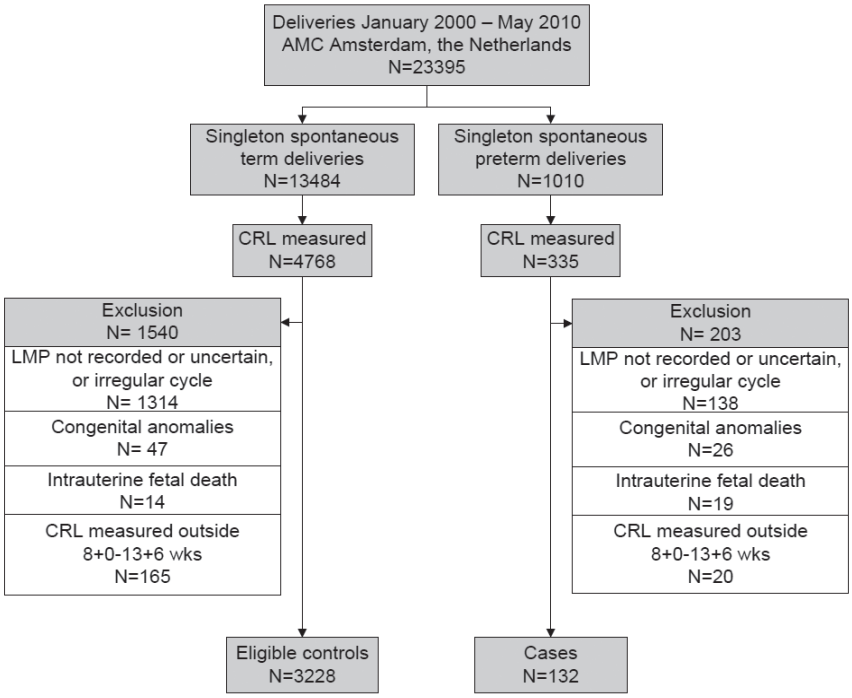

Figure 1 | Flow chart showing selection of study population. CRL, crown-rump length; LMP, last menstrual period.

Table 1 | Maternal and fetal characteristics of cases with preterm birth and controls with term births.

Characteristic	Cases (n=129)	Controls (n=129)	*P*-value
Maternal			
Age at ultrasound (years)	30.4 (6.3)	30.4 (6.1)	N.A.
Gestational age at ultrasound (weeks)	11+3 (1.5)	11+2 (1.3)	0.50 *
Body mass index (kg/m^2)†	22.7 (17.5-39.0)	23.6 (16.1-42.5)	0.69 *
Ethnicity			0.34 ‡
Caucasian	70 (54)	73 (56)	
African/black	15 (11)	8 (6)	
Indian	3 (2)	3 (2)	
South American	1 (1)	3 (2)	
Middle eastern	3 (2)	0 (0)	
Other/unknown	37 (28)	42 (32)	
Smoker	21 (24)	13 (16)	0.30 ‡
Alcohol intake	7 (8)	5 (6)	0.60 ‡
Parity †	1 (0-8)	2 (0-6)	<0.001
Previous pregnancies			
None/Nulliparous	15 (11)	15 (11)	N.A.
Any term birth ≥37 weeks	42 (33)	86 (67)	
Any preterm birth <37 weeks	104 (81)	104 (81)	N.A.
Any preterm birth 28-36 weeks	47(36)	47 (36)	
Any preterm birth 16-27 weeks	69 (53)	63 (49)	
Medical Indication for antenatal care			N.A.
Previous preterm birth	98 (76)	98 (76)	
Cervical or uterine anomalies	4 (3)	4 (3)	
Previous pre-eclampsia	1 (1)	1 (1)	
Hypertension	2 (2)	2 (2)	
Diabetes	1 (1)	1 (1)	
No medical indication/ patient's preference	15 (12)	15 (12)	
Other §	8 (6)	8 (6)	
Fetal			
First trimester crown-rump length (mm)	48 (11-86)	46 (11-74)	0.48 ‖
Male sex	75 (58)	67 (52)	0.31 ¶
Birth weight, (g) †	1192 (870-1500)	3290 (3000-3588)	<0.001 ‖
Birth weight, percentile†	31 (16-59)	27 (15-53)	0.48 ‖
Gestational age at birth (weeks) †	28+4 (24+0-32+0)	39+4 (37+0-41+6)	<0.001 ‖
Perinatal death	25 (19)	0	<0.001 ¶

Data are presented as means with standard deviations in parentheses or numbers with percentages in parentheses, unless indicated otherwise.

† Data presented as median (interquartile range).

N.A. = not applicable (matched for these variables)

Statistical tests used: *paired t-test; ‡ Chi square test ‖ Wilcoxon signed rank test; ¶ McNemar test;. § indications include HIV, asthma, epilepsy, inflammatory bowel disease, endocrine and systemic disorders.

In the logistic regression model including only CRL-MoM, no association with preterm birth was found: the odds ratio (OR) for preterm birth was 1.06, (95% CI 0.88-1.28), per 0.1 point increase in CRL-MoM. Adjusting for maternal age at ultrasound, parity and medical indication for antenatal care (the variables that were matched for) yielded comparable results: OR 1.07 (95% CI 0.88-1.30) per 0.1 point increase in CRL-MoM. Adding information to the regression model on smoking, fetal sex and maternal ethnicity, and in the final step timing of measurement, again did not influence the results: OR 1.06 (95% CI 0.87-1.30) and 1.10 (95% CI 0.89-1.36), respectively. Timing of measurement (gestational age at ultrasound as a continuous variable) did not significantly influence the model (*P*=0.593) and, accordingly, we did not find any significant interaction between timing of measurement and CRL-MoM in the prediction of preterm birth (*P*=0.724).

These findings were confirmed when we restricted our regression analyses to only the case-control pairs with a CRL measurement from 10+0 weeks onwards (93 cases and 93 controls). In the logistic regression model including only CRL-MoM, the OR for preterm birth was 1.06 (95% CI 0.85-1.32) per 0.1 point increase in CRL-MoM. Adjusting for maternal age at ultrasound, parity, medical indication for antenatal care, smoking, fetal sex and maternal ethnicity resulted in an OR for preterm birth of 1.07 (95% CI 0.83-1.37) per 0.1 point increase in CRL-MoM.

Figure 2 shows scatterplots of the distribution of predicted probabilities of preterm birth for CRL-MoM according to the regression model containing all information, i.e. CRL-MoM, maternal age at ultrasound, parity, medical indication for antenatal care, smoking, fetal sex, and maternal ethnicity. Across the ranges of CRL-MoMs, the predicted probabilities of preterm birth vary widely in the plot showing all data as well as the plots showing data before and after 10 weeks' gestation, and no apparent correlations can be observed.

Table 2 shows the percentages of short fetuses with short CRL in the case and control group with CRL-MoM below the 5th, 10th or 20th percentiles of the study population. There were more fetuses with CRL-MoM <5th percentile in the term birth (control) group, but this difference was not statistically significant (P=0.27). For fetuses with CRL-MoM <10th and <20th percentiles, there were no differences in percentages between the two groups

Table 2 | Short fetuses in the case and control group with MoMs CRL below the 5th, 10th and 20th percentile of the study population.

Case or control group	5th percentile	10th percentile	20th percentile
Preterm birth (cases)	4 (3.1)*	13 (10.0) ‡	26 (20.2) §
Term birth (controls)	8 (6.2)*	12 (9.3) ‡	26 (20.2) §

Data are presented as numbers with percentages in parentheses.

* p=0.27

‡ p=0.83

§ p> 0.99

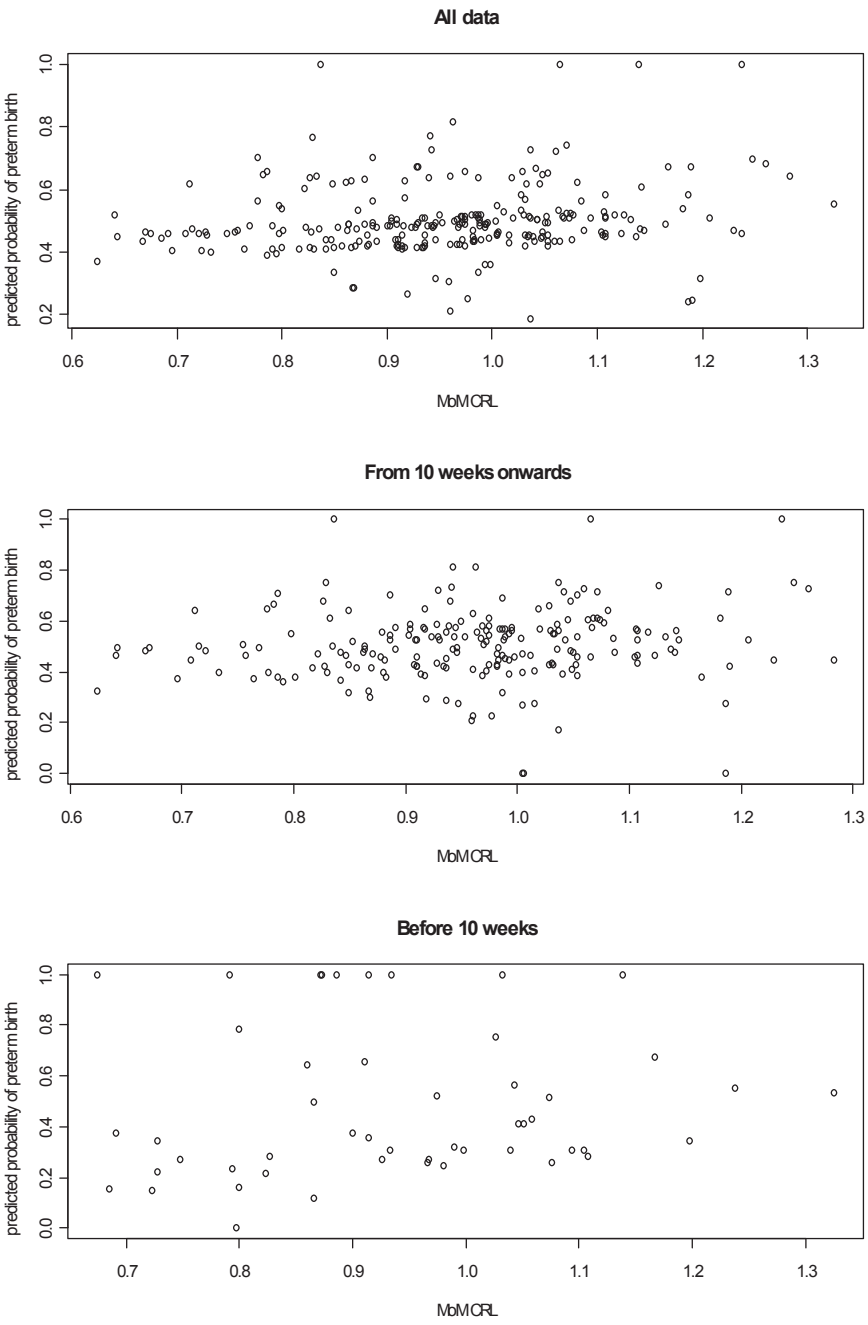

Figure 2 | Distribution of predicted probabilities of preterm birth across measured crown-rump length (CRL) (in multiples of the median, MoM) for all data (a) and for pregnancies examined after (b) and before (c) 10 weeks' gestation.

DISCUSSION

This study shows that a short CRL measurement in the first trimester is not associated with spontaneous preterm birth before 32 weeks' gestation. On the contrary, the point estimates show a trend towards fewer preterm births in fetuses with a shorter CRL.

Only extremely preterm births between 24 and 32 weeks' gestation were included in the study. The lower limit of 24 weeks is reflected in the Dutch guidelines that outline active care and management of the neonate from 24 weeks onwards. We chose this group of extreme preterm births based on our assumption that if an association between short CRL and preterm birth exists, it would be stronger in the extreme group or more likely to be found, and that if we did not find the association in this extreme group, it would be unlikely that such an association would exist for less severe cases of preterm birth. This constraint is a limitation to our study, since associations between short CRL and later, less severe preterm birth could not be evaluated.

Because of the nature of this study there were marked differences in birth weight and neonatal death between the groups, which were caused by the case group's comprising extremely preterm births in which lower birth weight (although mostly appropriate for gestational age) and increased mortality are to be expected (Table 1).

Our findings are inconsistent with those of previous studies.[6-8] The most important difference is that these studies defined preterm birth as a combination of both indicated and spontaneous preterm births, whereas our study specifically focused on the association between short CRL and spontaneous preterm births. The reasons for indicated preterm births include the presence of fetal growth restriction, and previous research has shown an association between short CRL and a birth weight below the 5th percentile for gestational age. [6,16] Thus, short CRL may be related to indicated preterm birth but not spontaneous preterm birth.

The paper by Mook-Kanamori *et al*.[6] which showed that fetuses with a shorter than expected CRL are at increased risk for preterm birth, gave rise to this study, in which we aimed to investigate the previously described association among spontaneous births only. The results of this study could be explained by the dating differences between the CRL and LMP methods if there were no association between CRL and preterm birth, and ultrasound were used for dating; if a fetus is shorter than would be expected based on LMP, the delivery date would be shifted after the dating scan and the fetus would be given more time to reach full term. However, if the delivery date based on LMP is used, the fetus would reach full term earlier and the probability of preterm birth is thus decreased.

In addition, the previous studies measured CRL from 10+0 to 13+6 weeks, whereas our study included CRL measured between 8+0 and 13+6 weeks. Yet timing of the ultrasound scan neither significantly influenced our regression model nor interacted with the effect of CRL-MoM on preterm birth, and restricting our analysis to case-control pairs who had had a CRL measurement from 10+0 weeks onwards yielded similar results. Another difference is that this study only considered early preterm births (<32 weeks), whereas others also included late preterm births, in which fetal growth restriction is supposed to play a bigger role.[17] However, the association between shorter than expected CRL and preterm birth has also been described in a group of preterm births prior to 32 weeks.[8]

Other methodological aspects of this study require comment. We performed paired analyses to compare baseline characteristics of the cases and controls (Table 1). Because the cases were individually matched to one control, the two groups are not independent. Treating our measurements as independent samples would artificially inflate sample size and would lead to inaccurate analyses.[18]

This study also has potential limitations. To be able to compare observed and expected CRL measurements, gestational age was calculated using LMP, which is known to be less accurate than that deducted from ultrasound.[19,20] Although dating errors are inherent to this type of study, we minimized them by including only women with a regular menstrual cycle and a reliable first day of last menstruation. Nevertheless, miscalculation of gestational age may have occurred, as the specific times of ovulation and implantation are unknown. In addition, selection bias may have occurred by excluding cases with uncertain LMP dates or the lack of a recorded CRL measurement. Part of the potential case group (Figure 1) consisted of women attending antenatal care in a midwifery practice until they were referred to our center for preterm labor. The majority did not have a recorded CRL measurement and were therefore excluded. Moreover, exclusion of fetuses with congenital anomalies or intrauterine fetal death, which were more prevalent in the case group than in the control group, might have led to selection bias.

Furthermore, our study population consisted of a selected group of women. As we selected women from our center's databases, almost all of them had a medical condition for which they attended for specialized obstetric care. Because we matched women with extreme preterm births to controls, in the control group many women had had a previous preterm birth. Although we adjusted for these factors, they will influence the generalizability of our results. In addition, the power of this study could be a potential weakness because of the relatively low number of patients included from our center.

Despite these limitations, the results of this study show that short CRL is not predictive of spontaneous preterm birth. The finding of a short CRL in early pregnancy does not indicate intensive monitoring for increased preterm birth risk. However, as the association found in previous research might be due to cases of indicated preterm birth, focusing research on the association between short CRL and pre-eclampsia and fetal growth restriction might yield more promising results for risk assessment in clinical practice.

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