Chapter 9

Mid-pregnancy cervical length in nulliparous women and its association with post-term delivery and intrapartum caesarean delivery

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Abstract

Objective: To evaluate the association between mid-pregnancy cervical length and post-term delivery and caesarean delivery during labour.

Study Design: In a multicentre cohort study, cervical length was measured in low-risk singleton pregnancies between 16 and 22 weeks of gestation. From this cohort we identified nulliparous women who delivered beyond 34 weeks and calculated cervical length quartiles. We performed logistic regression to compare the risk of post-term delivery and intrapartum caesarean delivery to cervical length quartiles, using the lowest quartile as a reference. We adjusted for induction of labour, maternal age, ethnicity, cephalic position, pre-existing hypertension and gestational age at delivery.

Results: We studied 5,321 nulliparous women. Women with cervical length in the 3rd and 4th quartile were more likely to deliver at 42^{+0} to 42^{+6} weeks (aOR 2.02, 95%CI 1.07-3.79 and aOR 1.97, 95%CI 1.06-3.67, respectively). The frequency of intrapartum caesarean delivery increased with cervical length quartile from 9.4% in the 1st to 14.9% in the 4th quartile (p= 0.01). This increase was only present in intrapartum caesarean delivery because of failure to progress and not because of fetal distress.

Conclusion: The longer the cervix at mid-trimester the higher the risk of both post-term delivery and intrapartum caesarean delivery.

Introduction

In an uncomplicated pregnancy the median gestational age of delivery is approximately 40 weeks.[1] Post-term pregnancy is defined by the World Health Organization as a pregnancy continuing beyond 42 completed weeks of gestation i.e. ≥ 294 days. Maternal and obstetrical complications increase as pregnancy progresses beyond term.[2-5] Moreover, neonates born after post-term pregnancies are at increased risk of perinatal mortality and morbidity. [3,6–8] Therefore, most guidelines advice to consider induction of labour between 41^{+0} weeks and 42^{+0} weeks of gestation.[9-11] Recent reviews [12-14] concluded that a policy of labour induction of pregnancies beyond term leads to better maternal and neonatal outcomes compared to expectant management. Worldwide the caesarean section rate is rising and varies considerably both between countries as well as between institutions.[15-17] Caesarean deliveries are associated with short- and long-term increased health risks for women and neonates.[18-21] Since both post-term pregnancies and caesarean deliveries are associated with increased maternal and perinatal morbidity, prediction of post-term delivery is important. For more than two decades cervical length and its role in predicting pregnancy outcome have been subject to investigation, mainly as a tool to define the preterm birth risk.[22,23] On the other hand, some studies found an increased risk of post-term delivery with increasing cervical length. In addition, two studies found a proportional increased risk of caesarean section with longer mid-trimester cervical length.[24,25] The caesarean delivery rate in the Netherlands is relative low (in 2013 the overall caesarean delivery rate was 16.4%, with an intrapartum caesarean delivery rate of 8.6%).[26] The studies in which an association was found between cervical length and caesarean deliveries had much higher caesarean delivery rates (Miller[24] 22% and Smith[25] 20%) compared to the Netherlands. In November 2009 we started a multicentre prospective cohort study in which we measured mid-trimester cervical length in order to evaluate cervical length measurement as a predictor on preterm birth in low risk women, the Triple P study.[27] The finding of a higher mean cervical length in our cohort study, the low incidence of cervical length ≤30 mm, compared to prior reports [27,28] as well as the relatively lower caesarean delivery rate in the Netherlands triggered us to perform a similar analysis on our data. In addition, we wanted to know whether an increase in caesarean deliveries, if observed, was caused by an increase in post-term pregnancies or whether it was also present in term pregnancies. The aim of the present study was to investigate if long cervical

length measured at mid-trimester is associated with post-term delivery and/or with an increased risk of intrapartum caesarean delivery.

Materials and methods

Procedure and recruitment

We performed a secondary analysis using data from the Triple P study, involving women with a singleton pregnancy who underwent a mid-trimester cervical length measurement during the routine anomaly scan at 16-22 weeks gestation.[27] Gestational age was determined based on first trimester sonography of crown-rump length according to our national guideline (NVOG).[30] The primary aim of the parent study was to study whether women with a short cervix would benefit from treatment with progesterone. The Triple P study included nulliparous and multiparous women with a singleton pregnancy. In this study, women < 18 years of age, women with a previous spontaneous preterm birth < 34 weeks, women with symptoms of threatened preterm labour (uterine contractions, ruptured membranes), with cervical or abdominal cerclage in situ, as well as women in which the fetus had known chromosomal or major structural anomalies were excluded. From this original cohort we identified all nulliparous women who had a cervical length measurement between 16^{+0}-21^{+6} weeks, and who delivered ≥34 weeks of gestation. Women with a planned caesarean delivery before labour and stillbirth before labour were excluded. Cervical length was measured by trained sonographers using a vaginal probe, placed in the anterior fornix of the vagina, without exerting undue pressure. The calipers were placed at the distance between the triangular area of echo density at the external os and the V-shaped notch at the internal os using a straight line. The cervix was measured according to the guidelines of the Dutch Society of Obstetrics and Gynaecology (NVOG) [31]and of the Fetal Medicine Foundation.[32]

Data collection

During the study, maternal date of birth, four digits of the postal code, expected date of delivery, date of measurement and cervical length were recorded in a web-based database. This information was used to link women to the Dutch Perinatal Registry database to obtain data on course and outcome of the pregnancy and delivery. The Dutch Perinatal Registry is a population-based database containing information

on 96% of all pregnancies, deliveries and (re)admissions until 28 days after birth.[31] All data contained in the Dutch Perinatal Registry are voluntarily recorded by the caregiver during prenatal care, delivery and the neonatal period. The data are sent annually to the national registry office, where a number of range and consistency checks are conducted. The Dutch Perinatal Registry board approved the linkage of their database for the purpose of the Triple P study (approval number 13.07). The Triple P was approved by the institutional review board of the Academic Medical Centre, Amsterdam, The Netherlands (MEC AMC 08-374, 08-328)

Outcome measures

We studied the rate of post-term deliveries, defined as delivery after 42 completed weeks of gestation, and delivery between 41+0 and 41+6 weeks of gestation. Other outcomes were intrapartum caesarean delivery, classified in caesarean section due to failure to progress and caesarean section due to suspected fetal distress.

Data analysis

We categorized cervical length of the included nulliparous women into four groups based on quartiles. Baseline characteristics of the cohort were compared between the cervical length quartiles using a chi-square test or a one-way Anova test when appropriate.

We expressed time to delivery, stratified by cervical length category, using a Kaplan Meier/ survival curve. When labour was induced, time to delivery was censored at the moment of induction. In addition, multivariable logistic regression analysis was performed to assess the association between cervical length quartile and delivery between 41+0 weeks and 41+6 weeks and between 42+0 weeks and 42+6 weeks of gestation. We adjusted for induction of labour, maternal age, ethnicity, pre-existing hypertension and cephalic position.

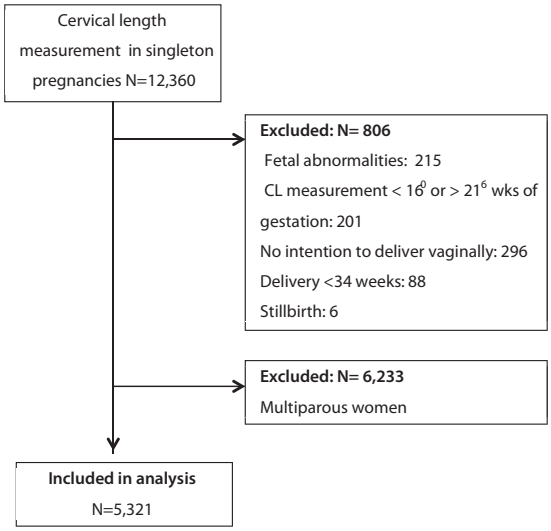
The number of caesarean deliveries was compared between the four quartiles of cervical length. Multivariable logistic regression was used to assess the association between cervical length quartile and caesarean delivery using the 1st quartile as a reference. We adjusted for induction of labour, maternal age, ethnicity, cephalic position, pre-existing hypertension and gestational age at delivery. The analysis was performed separately for caesarean delivery due to failure to progress and for suspected fetal distress. In addition, we performed the analysis for women delivering before 41 weeks to ensure that any found association between longer cervical length and caesarean delivery was not only due to post-term women.

A p-value below 0.05 was considered to indicate statistical significance. Analyses were performed using IBM SPSS Statistics (version 20.0, IBM Corp).

Results

Between November 2009 and August 2012 16,204 women had their cervical length measured. We were able to link data for 12,360 of the 16,204 women (74.4%) using the Dutch Perinatal Registry, thereby obtaining information on their outcome of pregnancy. There were no differences between the linked and unlinked women in median cervical length or interquartile range [43 mm (IQR 39-49 versus 43 mm (IQR 38-49) p=0.06]. Among those 12,360 women, 6,233 were multiparous women and 806 were excluded because they otherwise did not meet the inclusion criteria (figure 1).

Figure 1: Composition of study population



The final study population comprised 5,321 nulliparous women. The characteristics of the study population are presented in Table 1.

Table 1: Characteristics of the study population.

Characteristic*†	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	
	N=1197	N=1462	N=1290	N=1372	P
Cervical length (mm)	**35 (33-36)**	**40 (39-41)**	**45 (44-46)**	**51 (49-55)**	**0.0001**
Gestational age at cervical length (wk+day)	20+2 (20+0-20+5)	20+2 (20+0-20+4)	20+2 (20+0-20+4)	20+2 (20+0-20+4)	0.58
Maternal age (year)	**29 (4.7)**	**29 (4.6)**	**30 (4.5)**	**30(4.8)**	**<0.0001**
Non-Caucasian	**184 (15.4)**	**183 (12.5)**	**123 (9.5)**	**137 (10.0)**	**<0.0001**
Low SES	282 (23.8)	340 (23.4)	324 (25.3)	360 (26.4)	0.23
Method of conception					
Spontaneously	1116 (93.2)	1358 (92.9)	1181 (91.6)	1249 (91.0)	0.41
In Vitro Fertilisation	22(1.8)	30 (2.1)	30 (1.3)	33 (2.4)	
Other fertility treatments	59 (4.9)	74 (5.1)	79 (6.1)	90 (6.6)	
Pre-existing hypertension	16 (1.3)	8 (0.5)	21 (1.6)	19 (1.4)	0.05
Diabetes Mellitus	6 (0.5)	8 (0.5)	5 (0.4)	8 (0.6)	0.9
Gestational age at delivery (wk+day)	**39+5 (38+3-40+4)**	**40+0 (38+6-40+5)**	**40+1 (39+0-40+6)**	**40+1 (39+0-40+6)**	**<0.0001**
Induction of labour	240 (20.1)	289 (19.8)	239 (18.5)	273 (19.9)	0.75
Birth weight	**3316 (487)**	**3382 (476)**	**3439 (472)**	**3466 (504)**	**<0.0001**
Fetal position					
Cephalic	**1139 (96.4)**	**1399 (97.2)**	**1232 (97.7)**	**1323 (98.4)**	**0.034**
Breech	**40 (3.4)**	**35 (2.4)**	**24 (1.9)**	**18 (1.3)**	
Other	**3 (0.3)**	**6 (0.4)**	**5 (0.4)**	**4 (0.3)**	
Male fetal gender	594 (49.7)	723 (49.5)	684 (53.1)	700 (51.1)	0.23

*Data are median (interquartile range) or N (%)

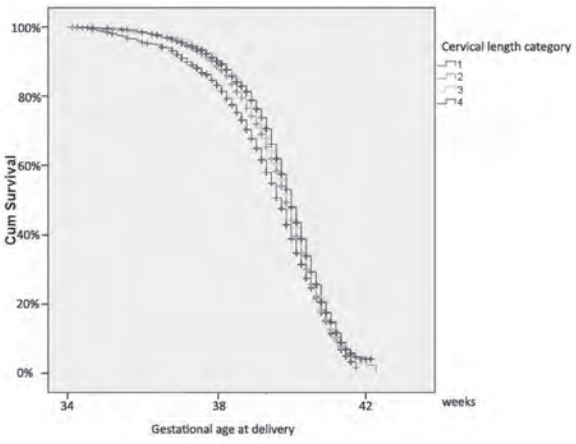
† Boldface data are statistically significant

The women with cervical length in the 1st quartile were significantly younger (29 year in the 1st quartile compared to 30 years in the 4th quartile, p<0.0001), more often of Non-Caucasian origin [184 (15.4%) versus 137 (10%), p<0.0001] and delivered at an earlier gestational age (39^{+5} versus 40^{+1}, p<0.0001).

Post-term pregnancy

The Kaplan-Meier curve displays time to delivery divided by cervical length quartiles, censored for inductions (figure 2).

Figure 2: Survival curve: Gestational age at delivery per cervical length quartile



The survival curves overlapped at the end and were not statistically significantly different (p=0.56). Women with cervical length in the 3rd and 4th quartile were more likely to deliver between 41^{+0} and 41^{+6} weeks of gestation (aOR 1.33, 95%CI 1.09-1.63, and aOR 1.29, 95%CI 1.05-1.57 respectively) and at 42^{+0} and 42^{+6} weeks of gestation (3rd quartile aOR 2.02, 95%CI 1.07-3.79, and 4th quartile aOR 1.97, 95%CI 1.06-3.67) compared to women with a cervical length in the 1stquartile (Table 2)

Table 2: Adjusted Odds ratio (aOR) for post-term delivery

Adjusted OR*	1st Quartile	95%CI	2nd Quartile	95%CI	3rd Quartile	95%CI	4th Quartile	95%CI
Delivery 41+0-41+6	Reference	Reference	1.1	0.90-1.34	**1.33**	**1.09-1.63**	**1.29**	**1.05-1.57**
Delivery 42+0-42+6	Reference	Reference	1.63	0.86-3.07	**2.02**	**1.07-3.79**	**1.97**	**1.06-3.67**

*Adjusted for induction of labour, maternal age, ethnicity, cephalic position and pre-existing hypertension
Boldface data are statistically significant

Table 3: Frequency and indication for caesarean delivery

	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
	N (%)*	N (%)	N (%)	N (%)
Caesarean delivery during labour	112 (9.4)	182 (12.4)	175 (13.6)	205 (14.9)
Indication: Fetal distress	29 (2.4)	37 (2.5)	33 (2.6)	50 (3.6)
Non-progression	66 (5.5)	103 (7.0)	112 (8.7)	119 (8.7)
Fetal distress and non-progression	4 (0.3)	21 (1.4)	12 (0.9)	17 (1.2)
Other	13 (1.1)	21 (1.4)	18 (1.4)	19 (1.4)

*Data of cervical length measurements N (%)

Table 4: Adjusted Odds ratio (aOR) for caesarean delivery

Adjusted OR*	1st Quartile	95%CI	2nd Quartile	95%CI	3rd Quartile	95%CI	4th Quartile	95%CI
Caesarean delivery during labour	Reference	Reference	**1.4**	**1.0-1.7**	**1.4**	**1.1-1.9**	**1.6**	**1.2-2.0**
Indication: Fetal distress	Reference	Reference	1.0	0.64-1.7	1.1	0.66-1.9	1.5	0.94-2.4
Non-progression	Reference	Reference	1.2	0.88-1.7	**1.5**	**1.1-2.0**	**1.4**	**1.0-1.9**

*Adjusted for induction of labour, maternal age, ethnicity, cephalic position, pre-existing hypertension and gestational age at delivery.
Boldface data are statistically significant

Caesarean delivery

Six hundred and seventy four women (12.7%) delivered by caesarean section, of whom 400 (59.3%) because of failure to progress, 149 (22%) because of suspected fetal distress and another 54 (8.0%) as a result of both failure to progress and suspected fetal distress (table 3). The frequency of caesarean delivery increased with cervical length quartile (9.4% in the 1st quartile, 12.4% in the 2nd, 13.6% in the 3rd, and 14.9% in the 4th quartile, p= 0.01)

Table 4 shows the adjusted odds ratios for all caesarean deliveries and separately for failure to progress or suspected fetal distress (adjusted for induction of labour, maternal age, ethnicity, cephalic position, pre-existing hypertension and gestational age at delivery). Women with cervical length in the 3rd and 4th quartile were at increased risk for caesarean delivery (aOR 1.4, 95%CI 1.1-1.9, and aOR 1.6, 95%CI 1.2-2.0 respectively). When the indication for the caesarean was failure to progress, longer cervical length was associated with an increased risk (aOR 3rd quartile 1.5, 95%CI 1.1-2.0 and aOR 4th quartile 1.4, 95%CI 1.0-1.9). In women who had a caesarean delivery for suspected fetal distress, this association was not present (aOR 3rd quartile 1.1, 95%CI 0.66-1.9 and aOR 4th quartile 1.5, 95%CI 0.94-2.4).

The association between longer cervical length and caesarean delivery remained significant after excluding all women with a pregnancy beyond 41 weeks (aOR 3rd quartile 1.5, 95%CI 1.1-2.0 and aOR 4th quartile 1.6, 95%CI 1.1-2.1).

Discussion

Main findings

This study shows that in nulliparous women, second trimester cervical length is associated with gestational age at onset of labour and with non-progressive labour. Women with a cervical length in the 4th quartile have a greater likelihood of post-term delivery as well as of caesarean compared with women in the 1st quartile. The increase in caesarean was only significant if the indication was failure to progress. Although the risk of caesarean was increased for women with a cervical length in the 3rd or 4th quartile, the majority of those women (85%) still delivered vaginally.

Strengths and weaknesses

The data from the present study are derived from a nationwide prospective cohort study in which mid-trimester cervical length was measured in order to identify

low-risk women at increased risk for preterm birth**.** Our cohort is composed of women receiving routine prenatal care at all obstetric care levels in the Netherlands (primary, - secondary- and tertiary care). We used mid-trimester cervical length as well as maternal characteristics and pregnancy outcome obtained by linkage with the database of the Dutch Perinatal Registry. After excluding multiparous women we obtained a large population representing a reliable cross section of pregnant women without prior pre- or post-term birth, or a history of caesarean delivery.

Our study has several limitations. First, we were not able to obtain pregnancy outcome in approximately 25% of our original study population because of inability to match our data to the Dutch Perinatal Registry database. Non-linkage was most probably due to incorrect digit entry and change of residence between ultrasound and birth. However, the median cervical length of the women who could not be linked to the Dutch Perinatal Registry did not significantly differ from that of the women who could be linked. Moreover, the Dutch Perinatal Registry contains perinatal outcome of 96% percent of all pregnancies that ended after 22 weeks of gestation, which makes it unlikely that the pregnancy outcomes of the not linked women could have changed our results. Second, in this study 29 ultrasound centres, 23 general- and seven university hospitals participated and in each centre/hospital the cervical length measurement was performed by various sonographers. The guidelines for cervical measurement of the Dutch Society of Obstetrics and Gynaecology. (NVOG)[31] were followed and explained to the sonographers prior to the participation. Furthermore, at the start of the study we developed a cervical length measurement e-learning module to enhance the knowledge and skills of the experienced sonographers[34] and to guarantee the quality of the cervical length measurements in our study. Burger et al.[35] described a variation of 2 mm or less in 87% of all measurements after implementation of a standard procedure for measuring cervical length, as we did.[34]Although the estimated date of delivery is mainly based on ultrasound in early pregnancy, which is associated with a reduction of misclassification in post-term pregnancies,[36,37] the rates of post-term births varies considerably between European countries.[38] This suggests that the policy regarding pregnancies beyond term is ambiguous. In an attempt to reduce the incidence of post-term pregnancy, induction of labour is generally considered, even in the absence of additional pregnancy complications. Zeitlin et al.[38] mention an association of lower rate of post-term pregnancies with increasing medical interventions in European countries. In The Netherlands there is an ongoing study comparing induction of labour versus expectant management

in women with impending post-term pregnancies.[39] The prediction of successful induction of labour in late-term or post-term pregnancies and the role of ultrasound cervical assessment for this purpose, has been subject of several studies.[14,40,41] At least two studies found an increased risk of (impending) post-term pregnancy and emergency caesarean section if cervical length measured >37 weeks of gestation is long.[39,40] Data from this study adds that cervical length even when measured at mid-trimester is associated with (impending) post-term pregnancy. In the Netherlands the overall rate of caesarean delivery rate is low in comparison with other Western countries[43]. According to the data of the Dutch Perinatal Registry[26] the rate of caesarean delivery during labour in pregnancies that ended after 22+0 weeks of gestation in 2013 was 8.6%. This is lower than in our study, which can be explained by the fact that we included only nulliparous women who delivered ≥34 weeks of gestation.

Comparison to other studies

Our study confirms the results of previous research between mid-trimester cervical length and caesarean delivery for failure to progress in nulliparous women.[24,25] Although the overall rate of caesarean delivery in our study was lower (12.7% versus 22.2% and 20.2%) , the same trend towards an increased risk of caesarean for failure to progress was seen with an increasing cervical length.

Statement of contribution

AV, BK wrote the first draft of the paper. BK and CE analyzed the data. AV, BK, EP and BW conceived the study. MO, CG, EM, MH, EP, BM critically revised the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be submitted.

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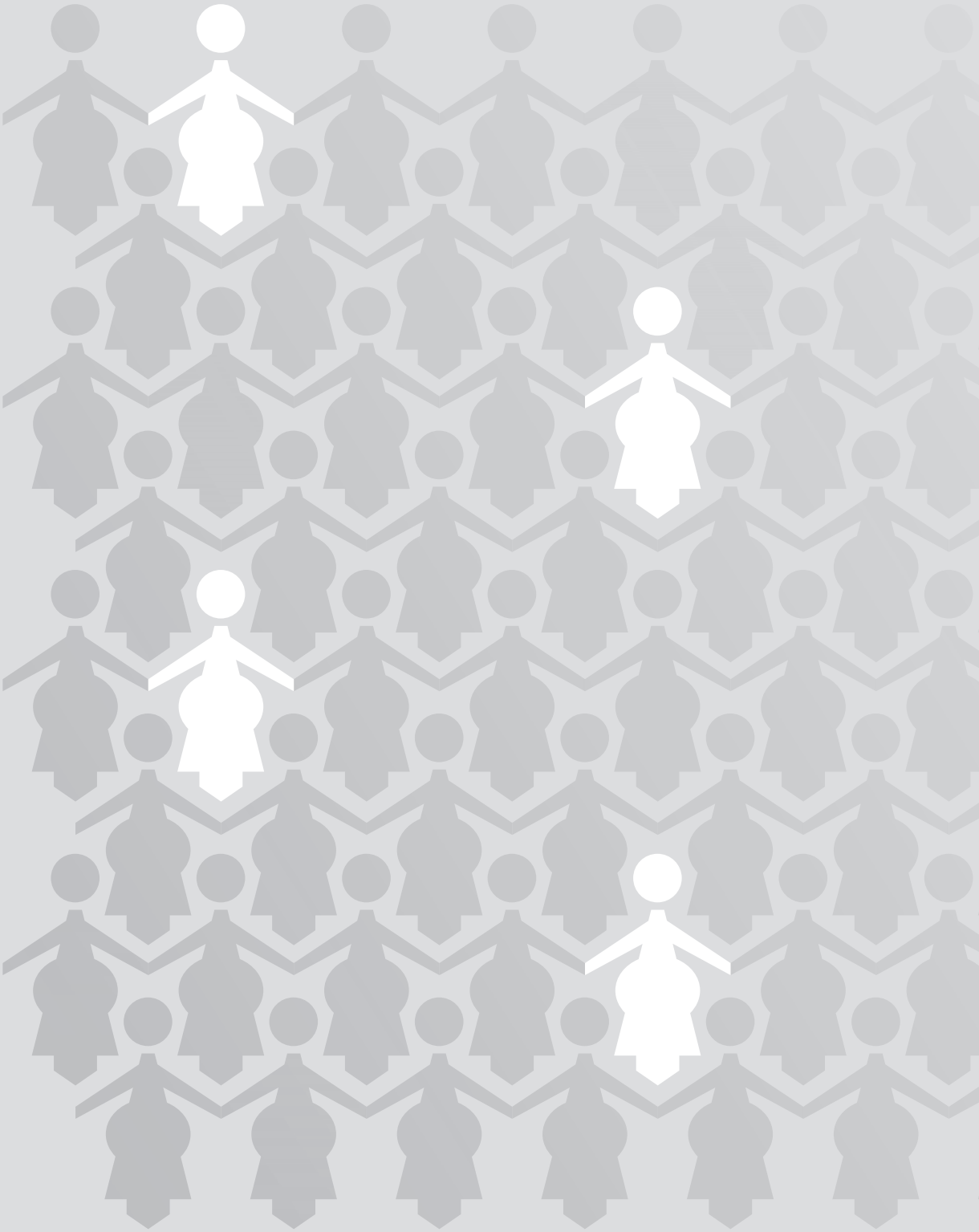

Part four:

Treatment to prevent preterm birth